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REVIEW

Has the era of individualised medicine arrived for antifungals? A review of antifungal pharmacogenomics

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Treatment or prophylaxis of invasive fungal infection in recipients of haemopoietic SCT (HSCT) may require management of coexistent malnutrition, organ dysfunction and GVHD, all of which create added potential for inter- and intra-patient variations in drug metabolism as well as drug interactions. Polymorphism is common in genes encoding pathway components of antifungal drug metabolism such as enzymes (cytochrome *P*450 (CYP450), glutathione *S*-transferase, *N*-acetyltransferase and uridine 5′-diphospho-glucuronosyltransferase), uptake transporters (organic cationic transporter, novel organic cationic transporter, organic anion transporter protein (OATP), organic anion transport (OAT), and peptide tranporter) and efflux transporters (breast cancer resistance protein, bile sale export pump (BSEP), multidrug and toxin extrusion type transporter, multidrug resistance protein (MRP), OAT, permeability glycoprotein (P-gp), and urate transporter). Specific polymorphisms may be generalised throughout a population or largely confined to ethnic groups. CYP450 enzymes, especially 2C9 and 2C19, exhibit extensive polymorphism and are central to the metabolism of azole antifungals and their interactions with other drugs including calcineurin inhibitors, cytotoxics and benzodiazepines. Polymorphism may ultimately affect drug efficacy: CYP2C19 variation leads to a fivefold variation in voriconazole levels between individuals. Anticipated routine provision of pharmacogenomic data in the future for new drugs, together with accumulating knowledge about established agents, challenge physicians to assimilate and apply that information to drug prescribing. Increasing availability of pharmacogenomic data may strengthen demand for rapid turnaround therapeutic drug monitoring of antifungal agents in HSCT recipients.

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Introduction

Achievements such as the Human Genome Project provide sound foundations for the development of 'individualised medicine'. Therapy tailored to individual genotype may enable prediction of efficacy and adverse events.[1] The Food and Drugs Administration clearly anticipates such developments and encourages the inclusion of pharmacogenomic data for new drugs[2] such as voriconazole, one of the first to include these data. Hence, it is timely to review current knowledge of pharmacogenomics of antifungal drugs and consider whether we might soon individually tailor therapy based on our understanding of genotypic variability in patients.

Absorption, distribution and metabolism of drugs

Table 1 presents an overview of factors affecting drug absorption, distribution and metabolism.

Gastric pH varies markedly within the population, with up to tenfold interindividual variation.[3] The impact of gastric pH on absorption of antifungal drugs is most clinically relevant for itraconazole and posaconazole.

Several antifungals are extensively protein bound, rendering them susceptible to variations in the levels of serum proteins, particularly albumin. Recipients of haemopoietic SCT (HSCT) are prone to malnutrition,[4] with consequent reduction in serum proteins. At least in the case of itraconazole, this results in increased levels of unbound drug.[5]

Structural variation in plasma proteins, such as is seen in the genetic variants of albumin,[6,7] may affect substrate binding,[8] but no relevant data are yet available as to whether this affects antifungal drugs.

Most cellular uptake of drugs occurs by passive diffusion, but some drugs are actively imported, requiring specific transporters (see Table 2) and energy expenditure. Most of the transporters exhibit genetic variants, the relative frequency of which varies with ethnicity.[9–11] This may be reflected in differing transport characteristics and drug levels among ethnic groups.[11] This is relevant to antifungal therapy as several antifungals are substrates or inhibitors of these transporters. The effect of genetic variability of transporters on the cyclodextrin carrier used to solubilise some antifungal drugs is currently unknown.

Table 1 Factors affecting the absorption, distribution and metabolism of drugs

Process	*Factors affecting the process*	*Comments*
Absorption (affects orally administered drugs)		
Dissolution in stomach	Gastric pH Presence of food	Gastric pH: lower and more acidic (enhances some drug absorption, e.g., *itraconazole capsules*) in men than women[124] in critically ill patients[125] Gastric pH: increased and less acidic (reduces some drug absorption, e.g., *posaconazole*) during fasting[126] use of H2-receptor agonists proton pump inhibitors[127]
Uptake from GI tract	Passive diffusion (no energy expenditure)	Affected by chemical composition of drug: Lipophilic drugs diffuse across cell membrane (e.g., *itraconazole, posaconazole*); hydrophilic drugs cross via aqueous channels (e.g., *fluconazole*)
	Active transport (requires expenditure of energy)	Other drugs, e.g., *amphipathic drugs*;[128] presence and activity of active transporters (e.g., P-*glycoprotein and itraconazole*)
Distribution		
Protein binding	Distribution to tissues affected by extent of protein binding of the drug in serum	*Fluconazole* and *voriconazole* are less protein bound, resulting in more extensive tissue penetration, such as central nervous system
Drug transporters	Presence and activity of transporters varies in different tissues (see Table 2)	SNPs in transporters may lead to reduced affinity for their substrates,[129] although there are currently no data for antifungal drugs
Metabolism		
First-pass metabolism (for orally administered drugs) and metabolism of many drugs	Distribution and activity of cytochrome *P*450 enzymes and P-glycoprotein in the liver and GI tract. Activity of CYP450 enzymes varies with age,[130] gender[131] and ethnicity[17]	Intestinal CYPs: 3A (80%), 2C9 (~14%)[132] Liver CYPs: 3A4/5 (29%), 2C (18%), 1A2 (13%)[133] Highest levels of 3A in duodenum and middle jejunum, declining in the distal jejunum and ileum[134] *Voriconazole* and *itraconazole* have extensive interactions via the CYP system

Abbreviations: CYP = cytochrome *P*450; GI = gastrointestinal; SNP = single-nucleotide polymorphism.

Table 2 Key uptake and efflux transporters

Uptake transporters	*Efflux transporters*	*Comments*
OCT[135,136] OCTN[137,138] OATP[139,140] OAT[137,140] PEPT[137,141]	BCRP[142,143] BSEP[144,145] MATE[146] MRP[142,147] OAT[148,149] P-glycoprotein[150,151] URAT[148,152]	Relative distribution of each transporter varies in intestines, kidney, liver and brain Genetic variants have been described for almost all the transporters listed here (references describing genetic variants are in bold). As several antifungals interact with these transporters *in vitro*, potentially they may interact *in vivo*.

Abbreviations: BCRP = breast cancer resistance protein; BSEP = bile salt export pump; MATE = Multidrug and toxin extrusion type transporter; MRP = multidrug resistance protein; OAT = organic anion transporter; OATP = organic anion transport protein; OCT = organic cation transporter; OCTN = novel organic cation transporter; PEPT = peptide transporter; URAT = urate transporter.

The cytochrome *P*450 (CYP450) enzyme system carries out phase I oxidative metabolism of a vast range of endogenous and exogenous substrates, including 75% of all drugs.[12] Drugs metabolised by the same CYP enzymes often interact,[13,14] and several websites detail the role of CYP enzymes in drug interactions (for example, http://bioinformatics.charite.de/supercyp/index.php?site = home, http://medicine.iupui.edu/clinpharm/ddis/ and http://www.drugbank.ca/). CYP expression varies with site and age (see Table 1) and, in addition, there may be up to 20-fold variability in CYP3A4 activity between individuals.[15] Thus, the same drug given orally to two patients may be subject to different levels of first-pass metabolism and hence achieve very different levels in the circulation. A further complication is the overlapping substrate specificities of CYP3A4 and permeability glycoprotein (P-gp).[16]

Interindividual variability of CYP450 enzyme activity is influenced by the frequent presence of allelic single-nucleotide polymorphisms (SNPs), some of which result in reduction or ablation of their metabolic activity. CYP2C19 has over 20 polymorphisms that result in truncated or inactive enzyme[17] and one that causes enhanced activity.[18] Other polymorphic cytochromes involved in antifungal drug metabolism include CYP2C9[19,20] and CYP3A4/5.[21,22] The prevalence of these polymorphisms varies in different populations and hence the likelihood of expressing a particular genotype/phenotype varies with ethnicity. In Caucasians, ~80% will have wild-type 2C9 alleles and ~20% the

commonly occurring variants, resulting in alterations in their substrate affinity.[23] For 2C19, the incidence of the 'poor metaboliser' phenotype associated with inactive 2C19 protein production is 2–6% in Caucasians, but 15–20% in Asians.[17]

Phase II metabolic processes, or conjugation reactions, are catalysed by a range of enzymes, including glutathione *S*-transferase, *N*-acetyltransferase and uridine 5′-diphosphoglucuronosyltransferase (UGT). These enzymes are genetically polymorphic,[24–26] with some of the resultant enzymes having decreased activity.[26,27] The CYP enzymes are central to the metabolism of azole antifungals, but some of the phase II enzymes have also been shown to be important for certain antifungal drugs.

Absorption, distribution, metabolism and elimination of antifungal drugs

Polyenes

Amphotericin B deoxycholate and the lipid formulations of amphotericin B. Amphotericin B deoxycholate is a polyene antifungal first licensed in the late 1950s, but now little used in its original formulation because of its toxicity. It binds to ergosterol in the fungal cell membrane, resulting in pore formation and leakage of cell constituents.[28]

The therapeutic advantages provided by the broad spectrum of activity, including yeasts and moulds, are offset by infusion-related toxicity and nephrotoxicity. In contrast, lipid formulations of amphotericin B maintain similar efficacy and are generally associated with fewer toxicities, but are significantly more expensive.[29] None of the amphotericin B preparations is absorbed orally and they must be given i.v. Amphotericin B is extensively protein bound in serum to lipoproteins via cholesterol,[30] serum albumin and human α1–acid glycoprotein,[31] but liposomal amphotericin largely remains within the liposomes in serum and hence does not appear to be significantly protein bound (Table 3).[31]

The metabolic pathway of amphotericin B and liposomal amphotericin is largely unknown,[28,32] rendering assessment of the impact of genetic variation somewhat speculative. In the case of amphotericin B deoxycholate, most of the drug is excreted unchanged in urine or faeces with $>90\%$ recovered within 7 days, suggesting that little metabolic breakdown occurs.[33] In contrast, $<10\%$ of liposomal amphotericin B is excreted unchanged within 7 days,[33] possibly reflecting slow tissue release.[34] No metabolites have been detected from either drug.

There are few data on the interaction of amphotericin B with the CYP system or drug transporters (see Table 4). Amphotericin B was associated with reduced levels of hepatic CYP3A4 in patients seropositive for HIV but this may have been because of nonspecific hepatocyte damage.[35] There are currently no data on the interaction of liposomal amphotericin and the CYP enzymes or drug transporters.

Amphotericin B deoxycholate reduces oral bioavailability of ciclosporin, an effect observed clinically.[36] This is mediated via increased expression of the multidrug resistance gene *MDR1* in the duodenum causing increased levels of the *MDR1* gene product P-gp,[36] but it is not known if liposomal amphotericin has a similar effect. This results in increased efflux of ciclosporin and reduced plasma levels. Interestingly, ciclosporin is itself an inhibitor of P-gp. The *MDR1* gene is polymorphic, raising the possibility of variation in the interaction with amphotericin B. These data suggest a possible interaction between amphotericin B deoxycholate and P-gp, and hence with the genetic polymorphisms seen in this transporter.

Overall, however, there is little evidence to support a clinically significant impact of pharmacogenomic variation upon the therapeutic effects of amphotericin B or its lipid formulations.

Triazole antifungals

The azoles have a common mode of action, inhibiting biosynthesis of ergosterol, critical to the integrity of the fungal cell membrane. Specifically, they inhibit 14α-sterol demethylase, an enzyme in the conversion pathway of lanosterol to ergosterol;[37] this demethylase is a member of the CYP450 superfamily found in fungi, designated CYP51A1.

Azoles are both inhibitors and substrates of various human CYP enzymes (Table 4). This may explain, in part, the plethora of drug interactions between azoles and several other groups of drugs, many of which are clinically relevant to the HSCT recipient.[38]

Fluconazole. Fluconazole is a triazole antifungal, with activity against *Cryptococcus* and many species of *Candida,* often with reduced activity against *Candida glabrata* and none against *Candida krusei*. It is not active against *Aspergillus*.

Available as oral and i.v. formulations, the oral bioavailability of fluconazole exceeds 90%,[39] and is unaffected by gastric pH,[40] food intake or gastrointestinal disease.[41]

It is hydrophilic with minimal protein binding and therefore achieves good tissue penetration into cerebrospinal fluid, saliva, sputum, vagina, skin[41] and brain tissue.[42] Elimination of fluconazole is predominantly renal with no circulating metabolites.[43]

Fluconazole inhibits, but is not a substrate of, several CYP enzymes (Table 4). It inhibits 2C9, 2C19 and to a lesser extent 3A4,[44,45] but not CYP1A2,[46] 2A6 or 2E1. Its ability to inhibit 2C9 and 2C19 causes potential drug interactions particularly relevant to HSCT recipients; for example, the interaction with CY may result in increased formation of toxic metabolites,[47] although others have noted a protective effect of co-administration.[48]

Fluconazole is both a substrate[49] and an inhibitor[50] of the UGT isoform, UGT2B7, the enzyme involved in its metabolism to the urinary metabolite fluconazole glucuronide.[43] It also inhibits UGT2B4, hence inhibiting, for example, the glucuronidation of codeine that may potentiate codeine-induced analgesia.[51]

The limited involvement of CYP and drug transporters in the uptake and metabolism of fluconazole means that their genetic variation has relatively little impact on fluconazole pharmacokinetics.

Itraconazole. Itraconazole is a triazole antifungal, with activity against *Candida* species (including some fluconazole-

Table 3 Licensed indications, absorption, distribution, metabolism and elimination of antifungal drugs

	Licensed indications[a]	*Absorption*	*Distribution*	*Metabolism*	*Elimination*	*Comments*
Amphotericin B deoxycholate	Systemic or deep mycoses; suspected or proven infection in febrile neutropenic patients	Poor oral bioavailability, hence i.v. only—complete absorption	95% protein bound[30]	Very little metabolic breakdown[33]	Largely unchanged in urine (21%) and bile (43%)[33]	Less often used clinically because of nephrotoxicity
Liposomal amphotericin B	Systemic or deep mycoses; suspected or proven infection in febrile neutropenic patients	Poor oral bioavailability, hence i.v. only—complete absorption	Most remains associated with the liposomes[31]	Very little metabolic breakdown[33]	Slow elimination: after 7 days only 5% excreted in urine and 4% in faeces—remaining drug thought to be in the tissues[33]	Complete elimination from tissues may take several weeks.[33] Aerosolised liposomal amphotericin B has shown promise in preventing aspergillosis[153] Dose adjustment in renal impairment or use alternative antifungal agent
Fluconazole	Invasive candidosis; treatment and prophylaxis of cryptococcosis; prophylaxis in immunocompromised patients	Good oral bioavailability >90%[39]	11–20% protein bound[39]	Limited metabolism[39]	Largely unchanged in urine (80%) with 11% metabolites[39]	In renal impairment dosage adjustment is required and may be required in hepatic impairment[154]
Itraconazole	Oral and oesophageal candidosis in immunocompromised patients; prophylaxis in haematology patients and HSCT recipients who are likely to become neutropenic	Gastric pH important; oral bioavailability better with solution than capsules[52,55]	99% protein bound[57]	Extensive hepatic metabolism via CYP3A4.[57] Hydroxy-itraconazole is an active metabolite	As metabolites via urine (35%) and faeces (54%); only 3–18% as parent drug detected in faeces[57]	The i.v. prep not recommended in severe renal impairment or haemodialysis; consider dose reduction in hepatic impairment
Voriconazole	Invasive aspergillosis; candidaemia in non-neutropenic patients; fluconazole-resistant invasive candidosis; serious infections caused by *Scedosporium* and *Fusarium*.	Good oral bioavailability >90%[61]	58% protein bound[155]	Largely hepatic. CYP2C19 and 3A4 are most important.[73] Higher incidence of 'poor metabolisers' in Asian,[17] SE Asian[156] and Pacific islander[157] populations	As metabolites in urine (78%) and faeces (23%); only 2% unchanged drug excreted in faeces[65]	The i.v. preparation not recommended in severe renal impairment or haemodialysis; dosage adjustment in hepatic impairment
Posaconazole	Prophylaxis in neutropenic patients undergoing chemotherapy for AML or MDS; patients who have received a HSCT and have GVHD. Invasive aspergillosis in patients intolerant of or refractory to amphotericin B or itraconazole.	Absorption is enhanced by concomitant fatty food intake[80] and acidic gastric environment[85]	99% protein bound[87]	Mainly via the UGT enzyme pathway, limited role for CYP[89]	66% excreted unchanged in faeces. Metabolites excreted in faeces (11%) and urine (14%)[89]	Caution in hepatic impairment
Caspofungin	Invasive candidosis, aspergillosis in patients refractory to or intolerant of amphotericin or itraconazole; empiric therapy in febrile neutropenic patients	Poor oral bioavailability, hence i.v. only—complete absorption	>90% protein bound, mainly to albumin[95] but varies between healthy individuals and patients	Peptide hydrolysis and *N*-acetylation[98]	Metabolites eliminated in urine (41%) and faeces (35%), with little drug excreted unchanged[98]	Dosage adjustment in hepatic impairment
Micafungin	Oesophageal and invasive candidosis; prophylaxis in adults undergoing allogeneic HSCT who are expected to become neutropenic; invasive candidosis; prophylaxis in children and adolescents	Poor oral bioavailability, hence i.v. only—complete absorption	99.8% protein bound, mainly to albumin and less to α1-acid glycoprotein[104]	Metabolised in liver, but not by CYP[103]	Metabolites excreted in faeces (>90%) and urine (8%); <1% of unchanged drug excreted in urine[103]	Avoid in severe hepatic impairment
Anidulafungin	Invasive candidosis in non-neutropenic patients	Poor oral bioavailability, hence i.v. only—complete absorption	>99% protein bound[158]	Slow chemical degradation, limited hepatic metabolism[110]	Mainly as metabolites in faeces (>90%) with ~10% excreted as unchanged drug[110]	No dosage adjustment required for renal or hepatic impairment

Abbreviations: CYP = cytochrome *P*450; HSCT = haemopoietic SCT; MDS = myelodysplastic syndrome; UGT = uridine 5′-diphospho-glucuronosyltransferase.
[a]All licensed indications and dosage adjustments are as in the British National Formulary, March 2011 (http://bnf.org/bnf/index.htm), or Ashley and Currie[159]

Table 4 Interactions of antifungals with cytochrome *P*450 enzymes and transporters

	Interaction	*Comments*
Amphotericin B	No inhibition of CYP3A4[160] or of P-gp *in vitro*.	Interaction with other transporters unknown.
Fluconazole	Potent inhibitor of CYP2C9 and CYP2C19,[44,45] and less so for CYP3A4.[160]	Interaction with ciclosporin via CYP inhibition causes increased ciclosporin levels, especially with oral fluconazole.[164,165]
	No inhibition of P-gp[160–162] or BCRP.[163]	
Itraconazole	Substrate for CYP3A4;[57] potent inhibitor of CYP3A4[160] and less so for CYP2C9, CYP2C19.[45]	CYP3A4 inhibition will affect metabolism of a variety of drugs to increase their levels (e.g., BU,[171] dexamethasone,[172] midazolam,[173] ciclosporin,[174] tacrolimus,[174] methyl-prednisolone[175]) or the levels of their metabolites. (e.g., CY[47]).
	Substrate[166] and inhibitor of P-gp.[160,161,167]	Inhibition of P-gp and, therefore P-gp-mediated cellular efflux, may cause increased VCR toxicity,[176] increased ciclosporin, tacrolimus and sirolimus levels,[177] reversal of resistance to vinblastine, DNR and doxorubicin.[178]
	Conflicting data as to inhibitory effect on OATP.[168,169]	
	Inhibitor of multidrug resistance protein 3.[170]	
	Inhibitor of BCRP.[163] No inhibition of NTCP or BSEP.[170]	
Voriconazole	Substrate for CYP2C19, CYP 3A4, CYP2C9.[73]	CYP interaction probably accounts for the interaction of voriconazole with many drugs, causing increased levels of tacrolimus,[180] ciclosporin,[181] increased VCR neurotoxicity[182] and reduced clearance of midazolam,[183] particularly the oral formulation of midazolam. Concomitant use of rifabutin,[184] an inducer of CYP and especially of CYP3A4, causes significant reduction in voriconazole levels.
	Inhibitor of CYP2C9, CYP2C19, CYP3A4 and CYP2B6.[179]	
	No inhibition of BCRP.[163]	
Posaconazole	Inhibitor of CYP3A4, but not a substrate of CYP.[185]	Inhibition of CYP3A4[185] results in increased levels of ciclosporin, tacrolimus[186] and midazolam.[185]
	Inhibitor and substrate of P-gp.[86]	Genetic polymorphisms of P-gp did not affect posaconazole exposure in healthy individuals.[86]
Caspofungin	Inhibitor of CYP3A4[58] and NCTP.[96] Not a substrate for CYP1A2, 2A6, 2C9, 2C19, 2D4 or 3A4.	CYP3A4 inhibition by caspofungin causes a 76% decrease in the metabolism of cytarabine.[187] CYP inducers (e.g., rifampin, nevirapine, efavirenz, carbamazepine, dexamethasome and phenytoin) induce the metabolism of caspofungin.[106]
	No inhibition of P-gp[96]	
	Substrate and inhibitor of OAT1B1.[96]	Rifampin may inhibit caspofungin tissue penetration via OATP1.[99]
Micafungin	Slight inhibition of CYP3A4.[160]	Micafungin inhibition of CYP3A4 increases ciclosporin levels in ~20% of patients,[188] but not tacrolimus.[189]
	No inhibition of P-gp.[160]	
Anidulafungin	No inhibition of CYP or OATP.[109]	Currently, no drug interactions are recorded.

Abbreviations: BCRP = breast cancer resistance protein; BSEP = bile salt export pump; CYP = cytochrome *P*450; NTCP = Na–taurocholate cotransporting polypeptide; OAT = organic anionic transporters; OATP = organic anionic transporting polypeptide; P-gp = permeability glycoprotein.

resistant species), *Aspergillus, Cryptococcus* and a range of other clinically important fungi.

Itraconazole is available as capsules, an oral solution and an i.v. infusion. The bioavailability of the capsules and oral solution varies significantly with dietary intake. Itraconazole capsules are maximally absorbed with food[52] and acidic drinks (for example, cola[53] or vitamin C drink[54]) at low gastric pH. Oral itraconazole solution has increased bioavailability (~30–35%) compared with the capsules, but in contrast to the capsules, is maximally absorbed during fasting.[55] Variations in gastric acidity and the widespread use of proton pump inhibitors in HSCT recipients may decrease absorption of itraconazole. Therefore, use of itraconazole oral solution in these patients, which produces higher serum trough concentrations,[56] is preferred.

Itraconazole is also a substrate or inhibitor of several drug transporters (Table 4).

Itraconazole is extensively protein bound, mainly to albumin,[57] and is predominantly metabolised in the liver, mainly by CYP3A4, for which it is both a substrate and an inhibitor.[58] More than 30 metabolites are formed,[57] including hydroxy-itraconazole,[59,60] all of which are inhibitors of CYP3A4 and have a higher affinity for CYP3A4 than itraconazole itself. This may explain the potency of CYP3A4 inhibition seen with itraconazole.[59]

Recently, itraconazole was shown to be a substrate for the phase II enzyme UGT1A4, with an affinity similar to that of the imidazole antifungal agents, and it may also be an inhibitor of UGT1A4.[49]

Itraconazole interacts with several genetically variable drug transporters and CYP enzymes, thus implicating them in the observed variability of itraconazole levels. Moreover, because CYP3A4 and P-glycoprotein also play a crucial role in the metabolism of many other drugs used in HSCT patients, this effect is likely to be compounded. Enhanced understanding of the pharmacogenomics of itraconazole will optimise itraconazole dosing as well as prediction of toxicities with other drugs.

Voriconazole. Voriconazole is a triazole antifungal, available as i.v. and oral formulations, with excellent oral bioavailability[61] and highly variable nonlinear pharmacokinetics.[62–64]

Excretion of voriconazole occurs predominantly via metabolites in the urine, with limited faecal excretion.[65]

Voriconazole has moderate plasma protein binding, but there are limited data on the interaction of voriconazole with the various drug transporters. Voriconazole may interact with CaMdr1p,[66] the yeast homologue of P-gp, and by implication human P-gp.

Genetic polymorphism in CYP2C19 accounts for 49% of the variance in clearance of voriconazole,[67] with recognition of 'poor metaboliser' and 'extensive metaboliser' phenotypes.[17] Levels of voriconazole in poor metabolisers

can be 4 to 5 times higher than those in extensive metabolisers.[68] A rapid metaboliser 2C19 phenotype has been described,[18] resulting in levels of voriconazole that are significantly lower than either the extensive or poor metaboliser phenotypes.[69] Interestingly, the coexistence of multiple CYP polymorphisms in the same patient do not necessarily have an additive effect on the metabolism of voriconazole.[70–72]

Metabolism of voriconazole results in several metabolites, the major circulating metabolite being the *N*-oxide of voriconazole,[65] formed predominantly by CYP3A4 and 2C19, with a smaller contribution from 2C9.[73] Production of the methyl hydroxylated metabolite is due solely to CYP3A4.[74] CYP450-mediated metabolism of voriconazole is responsible for ~75% of its oxidative metabolism. The remainder is due to flavin-containing mono-oxygenases[75] that also exhibit genetic polymorphism with resultant variations in catalytic activity.[76] Voriconazole is also a low-affinity substrate for UGT1A4 *in vitro*.[49]

An understanding of how genetic polymorphism affects voriconazole metabolism has been pivotal in explaining the pharmacokinetic variability observed in patients. The occurrence of genetic variants in the CYP alleles (Table 4) has a significant impact on the levels of drug achieved in those patients and probably upon the therapeutic efficacy of voriconazole.[77–79]

Posaconazole. Posaconazole is a triazole antifungal, currently only available as an oral suspension. Its bioavailability is significantly improved when taken with food (168% compared with the fasting state), especially if the food is high in fat (290% compared with the fasting state).[80] Doses up to 800 mg/day result in dose-proportional pharmacokinetics, but absorption is saturated at 800 mg/day.[81] Absorption of posaconazole is further improved by splitting the dose (200 mg four times daily compared with 400 mg twice daily) and administering with an acidic beverage or a nutritional supplement.[82,83] Concomitant dosing with cimetidine[84] or omeprazole[82] both decrease posaconazole serum trough levels, probably because of reduced gastric acidity, an effect likely to be seen with other H_2 receptor agonists or proton pump inhibitors.[85]

Data on interactions with transporters demonstrate that posaconazole is both a substrate and an inhibitor of P-gp.[86] The effect of SNPs in P-gp alleles was studied in 28 black and 28 Caucasian healthy volunteers dosed with 400 mg posaconazole twice daily after a meal. Individuals with a SNP resulting in reduced expression of P-gp ($n=13$) demonstrated no difference in the area under the curve compared with those with normal levels of P-gp ($n=43$). Therefore, the expression of SNPs in P-gp alleles had no effect on posaconazole pharmacokinetics in healthy individuals,[86] but whether this is also true in HSCT recipients, many of whom may have other issues related to absorption and reduced food intake, is not known. There are as yet no data on the interaction of posaconazole with other transporters in the setting of HSCT.

Posaconazole is extensively bound by plasma proteins mainly by serum albumin.[87]

In contrast to the other triazoles, posaconazole interacts with fewer CYP enzymes (Table 4), possibly explaining its narrower drug interaction range.

Posaconazole is excreted largely unchanged; there are no active metabolites[88] and the metabolites seen in urine are glucuronide conjugates,[89] produced by UGT1A4.[90] Genetic variants occur in the alleles for this enzyme,[91] some of which cause reduced catalytic activity.[92] Drug interactions may also occur via the UGT metabolic pathway, including that between posaconazole and phenytoin.[93]

Overall, it is likely that the effect of genetic variation on posaconazole pharmacokinetics is relatively small and more related to absorption than metabolism or elimination.

Echinocandins

The echinocandins inhibit β1,3-glucan synthetase, an enzyme involved in fungal cell wall synthesis, leading to increased cell wall permeability and fungal cell lysis. The lack of β1,3-glucan synthetase and cell wall in human cells explains the corresponding lack of toxicity seen with the echinocandins.[94]

Caspofungin. Caspofungin is an echinocandin antifungal that is dosed i.v. and is extensively protein bound in plasma, mainly to albumin. Its plasma profile is determined primarily by its rate of distribution from plasma into tissues, rather than by metabolism or excretion.[95] Uptake occurs into hepatocytes via an initial rapid reversible adsorption to the cell surface and a second slow phase of transport across the cell membrane,[95,96] mediated by organic anion transporter protein 1B1 (OATP1B1).[96] Interactions with other transporters are detailed in Table 4.

Biotransformation of caspofungin occurs primarily through hydrolysis, rather than by oxidative metabolism.[97] An initial open-ring metabolite is found in plasma, with subsequent peptide degradation resulting in low MW products found in urine. Within 4 weeks, 41% of the dose is excreted in urine and 35% in faeces[98] as metabolites.

Caspofungin is the echinocandin with most interaction with the CYP450 system (see Table 4).

Rifampin may inhibit the uptake of caspofungin into the tissues via OATP1, with trough levels 14–31% lower after multiple rifampin doses.[99] Genetic polymorphisms of OATP1B1[100] may affect the efficiency of uptake of caspofungin into the liver. However, there are no other known points at which genetic variability affects caspofungin, and hence pharmacogenomic analysis will be of minor importance in optimising use of this antifungal drug.

Micafungin. Micafungin is an echinocandin antifungal that is dosed i.v. It is mainly to bound to albumin and binding is independent of micafungin concentration.[101] Hepatocyte uptake is mediated by both active and passive mechanisms. Na–taurocholate cotransporting polypeptide (NTCP) is most important in uptake, whereas secretion across the canalicular hepatocyte membrane is mediated largely by BSEP (bile sale export pump). MRP3 (multidrug resistance protein 3) mediates transport of micafungin across the sinusoidal hepatocyte membrane. Biliary excretion rather than hepatic uptake is thought to be the rate-

limiting step in hepatic elimination of micafungin in humans.[102] Active transport is utilised for both uptake and excretion of micafungin and may be susceptible to genetic variability, as all the transporters involved in the process are known to be polymorphic.

Metabolism of micafungin occurs mainly in the liver, with inactive metabolites excreted in bile and urine.[103] Arylsulfatase is involved in micafungin metabolism,[104] and polymorphisms have been described.[105]

In general, however, pharmacogenomic analysis seems unlikely to add much to the clinical use of micafungin.

Anidulafungin. Anidulafungin is an echinocandin antifungal that is dosed i.v. Importantly, anidulafungin has no interactions described with any drug yet studied,[106] including rifampin.[107]

Anidulafungin is extensively bound by plasma proteins[108] and undergoes biotransformation, rather than metabolism, undergoing a slow, nonenzymatic degradation to inactive peptides.[97] Neither phase 1 nor phase 2 hepatic metabolism is involved in elimination of anidulafungin, nor is it a substrate, inducer or inhibitor of CYP450. At physiologically relevant concentrations it does not inhibit OATP.[109]

Elimination of anidulafungin is via bile in the faeces, with $<10\%$ of the drug excreted unchanged in the faeces and $<1\%$ in urine.[107,110]

Table 5 Assessment of laboratory service for provision of therapeutic drug monitoring (TDM)

Assay is fully validated[190,191] and is:
Selective
Accurate
Sensitive
Robust
Stable
Performs well in relevant quality assurance schemes
Small sample volume required
Clinical range defined
Assay performed regularly (ideally daily) and results communicated quickly
Cost per test appropriate to allow regular testing
Staff available to provide advice on interpretation of results and suggest corrective action if necessary

Genetic variation of CYP or phase II enzymes or the hepatic transporters is unlikely to affect anidulafungin pharmacokinetics, given their lack of interaction with anidulafungin, and hence pharmacogenomic analysis will not inform clinical use.

Therapeutic drug monitoring (TDM)

TDM is considered necessary for drugs with (1) unpredictable population pharmacokinetics, (2) a narrow therapeutic index and (3) a defined therapeutic range.[111] Amphotericin B, its lipid formulations and the echinocandins demonstrate predictable pharmacokinetics, and hence TDM is not required. The triazoles are the main agents where TDM is considered helpful in optimising treatment.[111–113] Although levels of fluconazole can vary significantly between patients, the variability is largely due to renal function, and hence doses are best adjusted according to creatinine clearance.[114] There is increasing evidence to support TDM in routine use of itraconazole, voriconazole and posaconazole.

The methods available for the measurement of drug levels include bioassays, high-performance liquid chromatography and liquid chromatography–mass spectrometry. Bioassays are inherently unreliable in patients receiving more than one antifungal drug, where the assay will usually only measure total antifungal activity and cannot separate out the activity due to each drug.[115] The presence of the microbiologically active metabolite of itraconazole, hydroxy-itraconazole, results in artificially elevated results in itraconazole bioassays.[112] Most laboratories now use either high-performance liquid chromatography or liquid chromatography–mass spectrometry as they are more sensitive, specific and have reduced analytical times. When properly validated, they are capable of measuring the level of an individual drug even in the presence of others. Assessment of a laboratory service for provision of TDM should ensure that the assays are performed regularly and results are communicated in a timely manner to ensure that they are relevant to patient management (see Table 5). The therapeutic ranges used vary between laboratories, but data are accumulating to suggest what the optimal ranges should be.

Table 6 Therapeutic drug monitoring ranges for itraconazole, voriconazole and posaconazole (pre-dose or trough levels)

Antifungal	*Target during prophylaxis (mg/L)*	*Target during treatment (mg/L)*	*Upper limit of nontoxic range (mg/L)*	*Studies from which levels are derived*
Itraconazole	0.5	0.5	4–5	Outcome better in aspergillosis,[192] cryptococcosis[193] and oral candidosis[194] with higher serum trough levels. In neutropenic patients, fewer breakthrough infections during prophylaxis with levels >0.5 mg/L[195]
Voriconazole	1–2	1–2	5–6	In invasive aspergillosis, favourable outcome correlated with levels >2.05 mg/L.[77] Improved outcome and lower fungal infection-related mortality with trough levels >2.2 mg/L[79] Liver toxicity seen in patients with levels >6 mg/L[63] and neurotoxicity seen in patients with levels >5.5 mg/L[78]
Posaconazole	0.7	1.25	Unknown	In prophylaxis, levels above 0.7 mg/L were associated with reduced clinical failure[196] In salvage therapy for invasive aspergillosis, response rate increased with increasing serum levels and in patients with average levels above 1.25 mg/L response rate was 75%[197]

Table 7 Suggested indications for therapeutic drug monitoring (TDM) of itraconazole, voriconazole and posaconazole

Indications for TDM
At 5–7 days after initiation of therapy or dose adjustment
If an interacting drug is started or stopped[a]
During prophylaxis if a breakthrough infection occurs
Uncertain drug compliance
Patient exhibits signs or symptoms of toxicity
Lack of response during treatment
Reduced oral absorption, for example, diarrhoea
Patient has inadequate oral nutrition[b]

[a]Precise timings of assay will be determined by the individual drug and concomitant medication.
[b]Not usually applicable for voriconazole because absorption is independent of gastric pH.

Table 6 summarises therapeutic ranges for itraconazole, voriconazole and posaconazole, and Table 7 lists the suggested indications for TDM.

Use of TDM is becoming more widespread and data from reference laboratories indicate that therapeutic levels are not achieved in a significant proportion of routine samples.[116–118] In compliant patients who have levels persistently out of range, there is an argument to support pharmacogenomic analysis of CYPs, for example, 2C19 in the case of voriconazole. In fact, some clinical laboratories are already providing this service.

The inability to predict serum levels from triazole drug doses, the significant potential for drug interactions, the effects of genetic variation on pharmacokinetics and the correlation between improved outcomes with higher serum levels all add to the weight of evidence supporting TDM in HSCT recipients.

Conclusions and future perspectives

Antifungal efficacy in invasive fungal infection is dependent on systemic drug exposure; therefore, maximising the absorption and distribution of antifungals to relevant tissues is essential for favourable treatment outcomes. The potential for genetically induced variation in metabolism of antifungal drugs, and the knock-on effect on drug interactions, remains largely theoretical, pending systematic laboratory evaluation. Such experience will clarify the relative importance of specific polymorphisms. However, there is already ample evidence of clinically relevant pharmacogenetic influence in the case of the azoles, particularly voriconazole. In contrast, its role in the use of amphotericin B and the echinocandins may be less important, because of their distinct metabolic and elimination pathways.

Genetic variation affects susceptibility to fungal infection,[119] metabolism and drug interactions of antifungals and, it is now emerging, the development of resistance to the azoles in *Aspergillus fumigatus*.[120,121] Unsurprisingly, mutations of fungal CYP51, a prime target of the triazoles, seem to mediate the predominant resistance pathways.[122]

Large-scale screening for SNPs in relevant human genes, using next-generation sequencing techniques,[123] is now feasible. As scientists unravel the journey of antifungal drugs through the body and the many enzymes and transporters encountered *en route*, we will benefit from a better understanding of how genetic variation affects pharmacokinetics. An individual will have a unique profile of susceptibility to invasive fungal infection,[119] metabolic handling of and response to antifungal therapy. Meaningful analysis of this genomic profile is a tantalising prospect on the horizon, if not quite within our grasp. The transition from horizon to clinic will depend upon a better understanding of the costs and benefits, particularly in the current economic climate.

Conflict of interest

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References

1 Cascorbi I. The promises of personalized medicine. *Eur J Clin Pharmacol* 2010; **66**: 749–754.
2 Andersson T, Flockhart DA, Goldstein DB, Huang SM, Kroetz DL, Milos PM *et al*. Drug-metabolizing enzymes: evidence for clinical utility of pharmacogenomic tests. *Clin Pharmacol Ther* 2005; **78**: 559–581.
3 Williams MP, Sercombe J, Hamilton MI, Pounder RE. A placebo-controlled trial to assess the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects. *Aliment Pharmacol Ther* 1998; **12**: 1079–1089.
4 Muscaritoli M, Grieco G, Capria S, Iori AP, Rossi FF. Nutritional and metabolic support in patients undergoing bone marrow transplantation. *Am J Clin Nutr* 2002; **75**: 183–190.
5 Arredondo G, Calvo R, Marcos F, Martinez-Jorda R, Suarez E. Protein binding of itraconazole and fluconazole in patients with cancer. *Int J Clin Pharmacol Ther* 1995; **33**: 449–452.
6 Madison J, Galliano M, Watkins S, Minchiotti L, Porta F, Rossi A *et al*. Genetic variants of human serum albumin in Italy: point mutants and a carboxyl-terminal variant. *Proc Natl Acad Sci USA* 1994; **91**: 6476–6480.
7 Franco MHLP, Brennan SO, Chua EKM, Kragh-Hansen U, Callegari-Jacques SM, Bezerra MZPJ *et al*. Albumin genetic variability in South America: population distribution and molecular studies. *Am J Hum Biol* 1999; **11**: 359–366.
8 Kragh-Hansen U, Brennan SO, Galliano M, Sugita O. Binding of warfarin, salicylate, and diazepam to genetic variants of human serum albumin with known mutations. *Mol Pharmacol* 1990; **37**: 238–242.
9 Chowbay B, Zhou S, Lee EJ. An interethnic comparison of polymorphisms of the genes encoding drug-metabolizing enzymes and drug transporters: experience in Singapore. *Drug Metab Rev* 2005; **37**: 327–378.

10 Cropp CD, Yee SW, Giacomini KM. Genetic variation in drug transporters in ethnic populations. *Clin Pharmacol Ther* 2008; **84**: 412–416.
11 Yasuda SU, Zhang L, Huang SM. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. *Clin Pharmacol Ther* 2008; **84**: 417–423.
12 Guengerich FP. Cytochrome p450 and chemical toxicology. *Chem Res Toxicol* 2008; **21**: 70–83.
13 Bruggemann RJM, Alffenaar JWC, Blijlevens NMA, Billaud EM, Kosterink JGW, Verweij PE *et al*. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. *Clin Infect Dis* 2009; **48**: 1441–1458.
14 Nivoix Y, Leveque D, Herbrecht R, Koffel JC, Beretz L, Ubeaud-Sequier G. The enzymatic basis of drug-drug interactions with systemic triazole antifungals. *Clin Pharmacokinet* 2008; **47**: 779–792.
15 Hsieh KP, Lin YY, Cheng CL, Lai ML, Lin MS, Siest JP *et al*. Novel mutations of CYP3A4 in Chinese. *Drug Metab Dispos* 2001; **29**: 268–273.
16 Wacher VJ, Wu CY, Benet LZ. Overlapping substrate specificities and tissue distribution of cytochrome P450 3A and P-glycoprotein: implications for drug delivery and activity in cancer chemotherapy. *Mol Carcinog* 1995; **13**: 129–134.
17 Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet* 2002; **41**: 913–958.
18 Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L *et al*. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther* 2006; **79**: 103–113.
19 Goldstein JA. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *Br J Clin Pharmacol* 2001; **52**: 349–355.
20 Xie HG, Prasad HC, Kim RB, Stein CM. CYP2C9 allelic variants: ethnic distribution and functional significance. *Adv Drug Deliv Rev* 2002; **54**: 1257–1270.
21 Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. *Adv Drug Deliv Rev* 2002; **54**: 1271–1294.
22 King BP, Leathart JB, Mutch E, Williams FM, Daly AK. CYP3A5 phenotype-genotype correlations in a British population. *Br J Clin Pharmacol* 2003; **55**: 625–629.
23 Stubbins MJ, Harries LW, Smith G, Tarbit MH, Wolf CR. Genetic analysis of the human cytochrome P450 CYP2C9 locus. *Pharmacogenetics* 1996; **6**: 429–439.
24 Pemble S, Schroeder KR, Spencer SR, Meyer DJ, Hallier E, Bolt HM *et al*. Human glutathione S-transferase theta (GSTT1): cDNA cloning and the characterization of a genetic polymorphism. *Biochem J* 1994; **300**(Part 1): 271–276.
25 Daly AK. Pharmacogenetics of the major polymorphic metabolizing enzymes. *Fundam Clin Pharmacol* 2003; **17**: 27–41.
26 Guillemette C, Ritter JK, Auyeung DJ, Kessler FK, Housman DE. Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human UGT1A7 gene. *Pharmacogenetics* 2000; **10**: 629–644.
27 Seidegard J, Vorachek WR, Pero RW, Pearson WR. Hereditary differences in the expression of the human glutathione transferase active on trans-stilbene oxide are due to a gene deletion. *Proc Natl Acad Sci USA* 1988; **85**: 7293–7297.
28 Dodds Ashley ES, Lewis R, Lewis JS, Martin C, Andes D. Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006; **43**: S28–S39.
29 Herbrecht R, Natarajan-Ame S, Nivoix Y, Letscher-Bru V. The lipid formulations of amphotericin B. *Expert Opin Pharmacother* 2003; **4**: 1277–1287.
30 Brajtburg J, Elberg S, Bolard J, Kobayashi GS, Levy RA, Ostlund Jr RE *et al*. Interaction of plasma proteins and lipoproteins with amphotericin B. *J Infect Dis* 1984; **149**: 986–997.
31 Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ. Plasma protein binding of amphotericin B and pharmacokinetics of bound versus unbound amphotericin B after administration of intravenous liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate. *Antimicrob Agents Chemother* 2002; **46**: 834–840.
32 Bartell A, Phatak A, Horn K, Postelnick MJ. Drug interactions involving antifungal drugs: time course and clinical significance. *Curr Fungal Infect Rep* 2010; **4**: 103–110.
33 Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ. Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. *Antimicrob Agents Chemother* 2002; **46**: 828–833.
34 Adler-Moore JP, Proffitt RT. AmBisome: liposomal formulation, structure, mechanism of action and pre-clinical experience. *J Antimicrob Chemother* 2002; **49**: 21–30.
35 Brockmeyer NH, Gambichler T, Bader A, Kreuter A, Kurowski M, Sander P *et al*. Impact of amphotericin B on the cytochrome P450 system in HIV-infected patients. *Eur J Med Res* 2004; **9**: 51–54.
36 Ishizaki J, Ito S, Jin M, Shimada T, Ishigaki T, Harasawa Y *et al*. Mechanism of decrease of oral bioavailability of cyclosporin A during immunotherapy upon coadministration of amphotericin B. *Biopharm Drug Dispos* 2008; **29**: 195–203.
37 Georgopapadakou NH. Antifungals: mechanism of action and resistance, established and novel drugs. *Curr Opin Microbiol* 1998; **1**: 547–557.
38 Egger SS, Meier S, Leu C, Christen S, Gratwohl A, Krahenbuhl S *et al*. Drug interactions and adverse events associated with antimycotic drugs used for invasive aspergillosis in hematopoietic SCT. *Bone Marrow Transplant* 2010; **45**: 1197–1203.
39 Humphrey MJ, Jevons S, Tarbit MH. Pharmacokinetic evaluation of UK-49,858, a metabolically stable triazole antifungal drug, in animals and humans. *Antimicrob Agents Chemother* 1985; **28**: 648–653.
40 Blum RA, D'Andrea DT, Florentino BM, Wilton JH, Hilligoss DM, Gardner MJ *et al*. Increased gastric pH and the bioavailability of fluconazole and ketoconazole. *Ann Intern Med* 1991; **114**: 755–757.
41 Brammer KW, Farrow PR, Faulkner JK. Pharmacokinetics and tissue penetration of fluconazole in humans. *Rev Infect Dis* 1990; **12**: 318–327.
42 Thaler F, Bernard B, Tod M, Jedynak CP, Petitjean O, Derome P *et al*. Fluconazole penetration in cerebral parenchyma in humans at steady state. *Antimicrob Agents Chemother* 1995; **39**: 1154–1156.
43 Brammer KW, Coakley AJ, Jezequel SG, Tarbit MH. The disposition and metabolism of [14C]fluconazole in humans. *Drug Metab Dispos* 1991; **19**: 764–767.
44 Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet* 2000; **38**: 111–180.
45 Niwa T, Shiraga T, Takagi A. Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 activities in human liver microsomes. *Biol Pharm Bull* 2005; **28**: 1805–1808.
46 Kunze KL, Wienkers LC, Thummel KE, Trager WF. Warfarin-fluconazole. I. Inhibition of the human cytochrome

P450-dependent metabolism of warfarin by fluconazole: in vitro studies. *Drug Metab Dispos* 1996; **24**: 414–421.
47 Marr KA, Leisenring W, Crippa F, Slattery JT, Corey L, Boeckh M *et al*. Cyclophosphamide metabolism is affected by azole antifungals. *Blood* 2004; **103**: 1557–1559.
48 Upton A, McCune JS, Kirby KA, Leisenring W, McDonald G, Batchelder A *et al*. Fluconazole coadministration concurrent with cyclophosphamide conditioning may reduce regimen-related toxicity postmyeloablative hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2007; **13**: 760–764.
49 Bourcier K, Hyland R, Kempshall S, Jones R, Maximilien J, Irvine N *et al*. Investigation into UDP-glucuronosyltransferase (UGT) enzyme kinetics of imidazole- and triazole-containing antifungal drugs in human liver microsomes and recombinant UGT enzymes. *Drug Metab Dispos* 2010; **38**: 923–929.
50 Uchaipichat V, Winner LK, Mackenzie PI, Elliot DJ, Williams JA, Miners JO. Quantitative prediction of in vivo inhibitory interactions involving glucuronidated drugs from in vitro data: the effect of fluconazole on zidovudine glucuronidation. *Br J Clin Pharmacol* 2006; **61**: 427–439.
51 Raungrut P, Uchaipichat V, Elliot DJ, Janchawee B, Somogyi AA, Miners JO. In vitro-in vivo extrapolation predicts drug-drug interactions arising from inhibition of codeine glucuronidation by dextropropoxyphene, fluconazole, ketoconazole, and methadone in humans. *J Pharmacol Exp Ther* 2010; **334**: 609–618.
52 van Peer A, Woestenborghs R, Heykants J, Gasparini R, Gauwenbergh G. The effects of food and dose on the oral systemic availability of itraconazole in healthy subjects. *Eur J Clin Pharmacol* 1989; **36**: 423–426.
53 Lange D, Pavao JH, Wu J, Klausner M. Effect of a cola beverage on the bioavailability of itraconazole in the presence of H2 blockers. *J Clin Pharmacol* 1997; **37**: 535–540.
54 Bae SK, Park SJ, Shim EJ, Mun JH, Kim EY, Shin JG *et al*. Increased oral bioavailability of itraconazole and its active metabolite, 7-hydroxyitraconazole, when coadministered with a vitamin C beverage in healthy participants. *J Clin Pharmacol* 2011; **51**: 444–451.
55 Barone JA, Moskovitz BL, Guarnieri J, Hassell AE, Colaizzi JL, Bierman RH *et al*. Enhanced bioavailability of itraconazole in hydroxypropyl-beta-cyclodextrin solution versus capsules in healthy volunteers. *Antimicrob Agents Chemother* 1998; **42**: 1862–1865.
56 Glasmacher A, Hahn C, Molitor E, Marklein G, Sauerbruch T, Schmidt-Wolf IG. Itraconazole trough concentrations in antifungal prophylaxis with six different dosing regimens using hydroxypropyl-beta-cyclodextrin oral solution or coated-pellet capsules. *Mycoses* 1999; **42**: 591–600.
57 Poirier JM, Cheymol G. Optimisation of itraconazole therapy using target drug concentrations. *Clin Pharmacokinet* 1998; **35**: 461–473.
58 Colburn DE, Giles FJ, Oladovich D, Smith JA. In vitro evaluation of cytochrome P450-mediated drug interactions between cytarabine, idarubicin, itraconazole and caspofungin. *Hematology* 2004; **9**: 217–221.
59 Isoherranen N, Kunze KL, Allen KE, Nelson WL, Thummel KE. Role of itraconazole metabolites in CYP3A4 inhibition. *Drug Metab Dispos* 2004; **32**: 1121–1131.
60 Templeton IE, Thummel KE, Kharasch ED, Kunze KL, Hoffer C, Nelson WL *et al*. Contribution of itraconazole metabolites to inhibition of CYP3A4 in vivo. *Clin Pharmacol Ther* 2008; **83**: 77–85.
61 Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. *Clin Infect Dis* 2003; **36**: 630–637.
62 Lazarus HM, Blumer JL, Yanovich S, Schlamm H, Romero A. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. *J Clin Pharmacol* 2002; **42**: 395–402.
63 Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E *et al*. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002; **34**: 563–571.
64 Bruggemann RJ, Blijlevens NM, Burger DM, Franke B, Troke PF, Donnelly JP. Pharmacokinetics and safety of 14 days intravenous voriconazole in allogeneic haematopoietic stem cell transplant recipients. *J Antimicrob Chemother* 2010; **65**: 107–113.
65 Roffey SJ, Cole S, Comby P, Gibson D, Jezequel SG, Nedderman AN *et al*. The disposition of voriconazole in mouse, rat, rabbit, guinea pig, dog, and human. *Drug Metab Dispos* 2003; **31**: 731–741.
66 Wakiec R, Prasad R, Morschhauser J, Barchiesi F, Borowski E, Milewski S. Voriconazole and multidrug resistance in Candida albicans. *Mycoses* 2007; **50**: 109–115.
67 Weiss J, Ten Hoevel MM, Burhenne J, Walter-Sack I, Hoffmann MM, Rengelshausen J *et al*. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. *J Clin Pharmacol* 2009; **49**: 196–204.
68 Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. *Clin Pharmacol Ther* 2004; **75**: 587–588.
69 Wang G, Lei HP, Li Z, Tan ZR, Guo D, Fan L *et al*. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. *Eur J Clin Pharmacol* 2009; **65**: 281–285.
70 Geist MJ, Egerer G, Burhenne J, Mikus G. Safety of voriconazole in a patient with CYP2C9*2/CYP2C9*2 genotype. *Antimicrob Agents Chemother* 2006; **50**: 3227–3228.
71 Liu P, Foster G, La Badie R, Somoza E, Sharma A. Pharmacokinetic interaction between voriconazole and methadone at steady state in patients on methadone therapy. *Antimicrob Agents Chemother* 2007; **51**: 110–118.
72 Mikus G, Schowel V, Drzewinska M, Rengelshausen J, Ding R, Riedel KD *et al*. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. *Clin Pharmacol Ther* 2006; **80**: 126–135.
73 Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. *Drug Metab Dispos* 2003; **31**: 540–547.
74 Murayama N, Imai N, Nakane T, Shimizu M, Yamazaki H. Roles of CYP3A4 and CYP2C19 in methyl hydroxylated and N-oxidized metabolite formation from voriconazole, a new anti-fungal agent, in human liver microsomes. *Biochem Pharmacol* 2007; **73**: 2020–2026.
75 Yanni SB, Annaert PP, Augustijns P, Bridges A, Gao Y, Benjamin Jr DK *et al*. Role of flavin-containing monooxygenase in oxidative metabolism of voriconazole by human liver microsomes. *Drug Metab Dispos* 2008; **36**: 1119–1125.
76 Cashman JR, Zhang J. Interindividual differences of human flavin-containing monooxygenase 3: genetic polymorphisms and functional variation. *Drug Metab Dispos* 2002; **30**: 1043–1052.
77 Smith J, Safdar N, Knasinski V, Simmons W, Bhavnani SM, Ambrose PG *et al*. Voriconazole therapeutic drug monitoring. *Antimicrob Agents Chemother* 2006; **50**: 1570–1572.
78 Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis* 2008; **46**: 201–211.

79 Miyakis S, van Hal SJ, Ray J, Marriott D. Voriconazole concentrations and outcome of invasive fungal infections. *Clin Microbiol Infect* 2010; **16**: 927–933.
80 Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. *Br J Clin Pharmacol* 2004; **57**: 218–222.
81 Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrob Agents Chemother* 2003; **47**: 2788–2795.
82 Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. *Antimicrob Agents Chemother* 2009; **53**: 958–966.
83 Sansone-Parsons A, Krishna G, Calzetta A, Wexler D, Kantesaria B, Rosenberg MA *et al*. Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers. *Antimicrob Agents Chemother* 2006; **50**: 1881–1883.
84 Courtney R, Wexler D, Statkevich P, Laughlin M. Effect of cimetidine on the pharmacokinetics of posaconazole in healthy volunteers. *Intersci Conf Antimicrob Agents Chemother* 2002 Abstract A-1838.
85 Nagappan V, Deresinski S. Letter—Reply to Cornely and Ullmann and to Jain and Pottinger. *Clin Infect Dis* 2008; **46**: 1627–1628.
86 Courtney R, Sansone-Parsons A, Devlin D, Soni P, Laughlin M, Simon J. P-Glycoprotein (P-gp) expression and genotype: exploratory analysis of posaconazole (POS) in healthy volunteers. *Intersci Conf Antimicrob Agents Chemother* 2004 Abstract A-40.
87 Li Y, Theuretzbacher U, Clancy CJ, Nguyen MH, Derendorf H. Pharmacokinetic/pharmacodynamic profile of posaconazole. *Clin Pharmacokinet* 2010; **49**: 379–396.
88 Kim H, Kumari P, Laughlin M, Hilbert MJ, Indelicato SR, Lim J *et al*. Use of high-performance liquid chromatographic and microbiological analyses for evaluating the presence or absence of active metabolites of the antifungal posaconazole in human plasma. *J Chromatogr A* 2003; **987**: 243–248.
89 Krieter P, Flannery B, Musick T, Gohdes M, Martinho M, Courtney R. Disposition of posaconazole following single-dose oral administration in healthy subjects. *Antimicrob Agents Chemother* 2004; **48**: 3543–3551.
90 Ghosal A, Hapangama N, Yuan Y, Achanfuo-Yeboah J, Iannucci R, Chowdhury S *et al*. Identification of human UDP-glucuronosyltransferase enzyme(s) responsible for the glucuronidation of posaconazole (Noxafil). *Drug Metab Dispos* 2004; **32**: 267–271.
91 Benoit-Biancamano MO, Adam JP, Bernard O, Court MH, Leblanc MH, Caron P *et al*. A pharmacogenetics study of the human glucuronosyltransferase UGT1A4. *Pharmacogenet Genomics* 2009; **19**: 945–954.
92 Mori A, Maruo Y, Iwai M, Sato H, Takeuchi Y. UDP-glucuronosyltransferase 1A4 polymorphisms in a Japanese population and kinetics of clozapine glucuronidation. *Drug Metab Dispos* 2005; **33**: 672–675.
93 Krishna G, Sansone-Parsons A, Kantesaria B. Drug interaction assessment following concomitant administration of posaconazole and phenytoin in healthy men. *Curr Med Res Opin* 2007; **23**: 1415–1422.
94 Denning DW. Echinocandin antifungal drugs. *Lancet* 2003; **363**: 1142–1151.
95 Stone JA, Xu X, Winchell GA, Deutsch PJ, Pearson PG, Migoya EM *et al*. Disposition of caspofungin: role of distribution in determining pharmacokinetics in plasma. *Antimicrob Agents Chemother* 2004; **48**: 815–823.
96 Sandhu P, Lee W, Xu X, Leake BF, Yamazaki M, Stone JA *et al*. Hepatic uptake of the novel antifungal agent caspofungin. *Drug Metab Dispos* 2005; **33**: 676–682.
97 Wagner C, Graninger W, Presterl E, Joukhadar C. The echinocandins: comparison of their pharmacokinetics, pharmacodynamics and clinical applications. *Pharmacology* 2006; **78**: 161–177.
98 Balani SK, Xu X, Arison BH, Silva MV, Gries A, DeLuna FA *et al*. Metabolites of caspofungin acetate, a potent antifungal agent, in human plasma and urine. *Drug Metab Dispos* 2000; **28**: 1274–1278.
99 Stone JA, Migoya EM, Hickey L, Winchell GA, Deutsch PJ, Ghosh K *et al*. Potential for interactions between caspofungin and nelfinavir or rifampin. *Antimicrob Agents Chemother* 2004; **48**: 4306–4314.
100 Vormfelde SV, Toliat MR, Schirmer M, Meineke I, Nurnberg P, Brockmoller J. The polymorphisms Asn130Asp and Val174Ala in OATP1B1 and the CYP2C9 allele *3 independently affect torsemide pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2008; **83**: 815–817.
101 Chandrasekar PH, Sobel JD. Micafungin: a new echinocandin. *Clin Infect Dis* 2006; **42**: 1171–1178.
102 Yanni SB, Augustijns PF, Benjamin Jr DK, Brouwer KL, Thakker DR, Annaert PP. In vitro investigation of the hepatobiliary disposition mechanisms of the antifungal agent micafungin in humans and rats. *Drug Metab Dispos* 2010; **38**: 1848–1856.
103 Groll AH, Stergiopoulou T, Roilides E, Walsh TJ. Micafungin: pharmacology, experimental therapeutics and clinical applications. *Expert Opin Investig Drugs* 2005; **14**: 489–509.
104 Hebert MF, Smith HE, Marbury TC, Swan SK, Smith WB, Townsend RW *et al*. Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. *J Clin Pharmacol* 2005; **45**: 1145–1152.
105 Gort L, Coll MJ, Chabas A. Identification of 12 novel mutations and two new polymorphisms in the arylsulfatase A gene: haplotype and genotype-phenotype correlation studies in Spanish metachromatic leukodystrophy patients. *Hum Mutat* 1999; **14**: 240–248.
106 Sucher AJ, Chahine EB, Balcer HE. Echinocandins: the newest class of antifungals. *Ann Pharmacother* 2009; **43**: 1647–1657.
107 Dowell JA, Knebel W, Ludden T, Stogniew M, Krause D, Henkel T. Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. *J Clin Pharmacol* 2004; **44**: 590–598.
108 Inskeep PB, Lin J. Plasma protein binding of anidulafungin is similar to other major echinocandins. *18th Eur Congr Clin Microbiol Infect Dis* 2008 Abstract P1048.
109 Inskeep PB, Walsky RL, Feng B, Campbell S. Lack of anidulafungin interactions with CYP enzymes and transporters in in vivo and in vitro systems. *18th Eur Congr Clin Microbiol Infect Dis* 2008 Abstract P1049.
110 Damle BD, Dowell JA, Walsky RL, Weber GL, Stogniew M, Inskeep PB. In vitro and in vivo studies to characterize the clearance mechanism and potential cytochrome P450 interactions of anidulafungin. *Antimicrob Agents Chemother* 2009; **53**: 1149–1156.
111 Lewis RE. Antifungal therapeutic drug monitoring. *Curr Fungal Infect Rep* 2010; **4**: 158–167.
112 Goodwin ML, Drew RH. Antifungal serum concentration monitoring: an update. *J Antimicrob Chemother* 2008; **61**: 17–25.
113 Hussaini T, Ruping MJ, Farowski F, Vehreschild JJ, Cornely OA. Therapeutic drug monitoring of voriconazole and posaconazole. *Pharmacotherapy* 2011; **31**: 214–225.

114 Cota JM, Burgess DS. Antifungal dose adjustment in renal and hepatic dysfunction: pharmacokinetic and pharmacodynamic considerations. *Curr Fungal Infect Rep* 2010; **4**: 120–128.
115 Bruggemann RJ, Touw DJ, Aarnoutse RE, Verweij PE, Burger DM. International interlaboratory proficiency testing program for measurement of azole antifungal plasma concentrations. *Antimicrob Agents Chemother* 2009; **53**: 303–305.
116 Thompson GR, Rinaldi MG, Pennick G, Dorsey SA, Patterson TF, Lewis JS. Posaconazole therapeutic drug monitoring: a reference laboratory experience. *Antimicrob Agents Chemother* 2009; **53**: 2223–2224.
117 Hassan A, Burhenne J, Riedel KD, Weiss J, Mikus G, Haefeli WE *et al*. Modulators of very low voriconazole concentrations in routine therapeutic drug monitoring. *Ther Drug Monit* 2011; **33**: 86–93.
118 Bryant AM, Slain D, Cumpston A, Craig M. A post-marketing evaluation of posaconazole plasma concentrations in neutropenic patients with haematological malignancy receiving posaconazole prophylaxis. *Int J Antimicrob Agents* 2011; **37**: 266–269.
119 Bochud PY, Chien JW, Marr KA, Leisenring W, Upton A, Janer M *et al*. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. *N Engl J Med* 2008; **359**: 1766–1777.
120 Howard SJ, Arendrup MC. Acquired antifungal drug resistance in Aspergillus fumigatus: epidemiology and detection. *Med Mycol* 2011; **49**(Suppl 1): S90–S95.
121 Verweij PE, Snelders E, Kema GH, Mellado E, Melchers WJ. Azole resistance in Aspergillus fumigatus: a side-effect of environmental fungicide use? *Lancet Infect Dis* 2009; **9**: 789–795.
122 Snelders E, Van Der Lee HA, Kuijpers J, Rijs AJ, Varga J, Samson RA *et al*. Emergence of azole resistance in Aspergillus fumigatus and spread of a single resistance mechanism. *PLoS Med* 2008; **5**: e219.
123 Mardis ER. Next-generation DNA sequencing methods. *Annu Rev Genomics Hum Genet* 2008; **9**: 387–402.
124 Feldman M, Barnett C. Fasting gastric pH and its relationship to true hypochlorhydria in humans. *Dig Dis Sci* 1991; **36**: 866–869.
125 Welage LS, Carver PL, Revankar S, Pierson C, Kauffman CA. Alterations in gastric acidity in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1995; **21**: 1431–1438.
126 Barone JA, Koh JG, Bierman RH, Colaizzi JL, Swanson KA, Gaffar MC *et al*. Food interaction and steady-state pharmacokinetics of itraconazole capsules in healthy male volunteers. *Antimicrob Agents Chemother* 1993; **37**: 778–784.
127 Jaruratanasirikul S, Sriwiriyajan S. Effect of omeprazole on the pharmacokinetics of itraconazole. *Eur J Clin Pharmacol* 1998; **54**: 159–161.
128 Hagenbuch B. Drug uptake systems in liver and kidney: a historic perspective. *Clin Pharmacol Ther* 2010; **87**: 39–47.
129 Shu Y, Sheardown SA, Brown C, Owen RP, Zhang S, Castro RA *et al*. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. *J Clin Invest* 2007; **117**: 1422–1431.
130 Kinirons MT, O'Mahony MS. Drug metabolism and ageing. *Br J Clin Pharmacol* 2004; **57**: 540–544.
131 Parkinson A, Mudra DR, Johnson C, Dwyer A, Carroll KM. The effects of gender, age, ethnicity, and liver cirrhosis on cytochrome P450 enzyme activity in human liver microsomes and inducibility in cultured human hepatocytes. *Toxicol Appl Pharmacol* 2004; **199**: 193–209.
132 Paine MF, Hart HL, Ludington SS, Haining RL, Rettie AE, Zeldin DC. The human intestinal cytochrome P450 "pie". *Drug Metab Dispos* 2006; **34**: 880–886.
133 Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther* 1994; **270**: 414–423.
134 Paine MF, Khalighi M, Fisher JM, Shen DD, Kunze KL, Marsh CL *et al*. Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. *J Pharmacol Exp Ther* 1997; **283**: 1552–1562.
135 Lin CJ, Tai Y, Huang MT, Tsai YF, Hsu HJ, Tzen KY *et al*. Cellular localization of the organic cation transporters, OCT1 and OCT2, in brain microvessel endothelial cells and its implication for MPTP transport across the blood-brain barrier and MPTP-induced dopaminergic toxicity in rodents. *J Neurochem* 2010; **114**: 717–727.
136 Shikata E, Yamamoto R, Takane H, Shigemasa C, Ikeda T, Otsubo K *et al*. Human organic cation transporter (OCT1 and OCT2) gene polymorphisms and therapeutic effects of metformin. *J Hum Genet* 2007; **52**: 117–122.
137 Terada T, Inui K-I. Gene expression and regulation of drug transporters in the intestine and kidney. *Biochem Pharmacol* 2007; **73**: 440–449.
138 Ferguson LR, Han DY, Heubner C, Petermann I, Demmers P, McCulloch A *et al*. Single nucleotide polymorphisms in *IL4*, *OCTN1* and *OCTN2* genes in association with inflammatory bowel disease phenotypes in a caucasian population in canterbury, New Zealand. *Open Gastroenterol J* 2008; **2**: 50–56.
139 Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol* 2009; **158**: 693–705.
140 Iida A, Saito S, Sekine A, Mishima C, Kondo K, Kitamura Y *et al*. Catalog of 258 single-nucleotide polymorphisms (SNPs) in genes encoding three organic anion transporters, three organic anion-transporting polypeptides, and three NAD-H:ubiquinone oxidoreductase flavoproteins. *J Hum Genet* 2001; **46**: 668–683.
141 Zhang L, Zhang Y, Huang SM. Scientific and regulatory perspectives on metabolizing enzyme-transporter interplay and its role in drug interactions: challenges in predicting drug interactions. *Mol Pharm* 2004; **6**: 1766–1774.
142 Hilgendorf C, Ahlin G, Seithel A, Artursson P, Ungell AL, Karlsson J. Expression of thirty-six drug transporter genes in human intestine, liver, kidney, and organotypic cell lines. *Drug Metab Dispos* 2007; **35**: 1333–1340.
143 Zamber CP, Lamba JK, Yasuda K, Farnum J, Thummel K, Schuetz JD *et al*. Natural allelic variants of breast cancer resistance protein (BCRP) and their relationship to BCRP expression in human intestine. *Pharmacogenetics* 2003; **13**: 19–28.
144 Chandra P, Brouwer KLR. The complexities of hepatic drug transport: current knowledge and emerging concepts. *Pharm Res* 2004; **21**: 719–735.
145 Ho RH, Leake BF, Kilkenny DM, Meyer Zu Schwabedissen HE, Glaeser H, Kroetz DL *et al*. Polymorphic variants in the human bile salt export pump (BSEP; ABCB11): functional characterization and interindividual variability. *Pharmacogenet Genomics* 2010; **20**: 45–57.
146 Meyer Zu Schwabedissen HE, Verstuyft C, Kroemer HK, Becquemont L, Kim RB. Human multidrug and toxin extrusion 1 (MATE1/SLC47A1) transporter: functional characterization, interaction with OCT2 (SLC22A2), and single nucleotide polymorphisms. *Am J Physiol Renal Physiol* 2010; **298**: F997–F1005.
147 Keitel V, Kartenbeck J, Nies AT, Spring H, Brom M, Keppler D. Impaired protein maturation of the conjugate

export pump multidrug resistance protein 2 as a consequence of a deletion mutation in Dubin-Johnson syndrome. *Hepatology* 2000; **32**: 1317–1328.
148 El-Sheikh AAK, Masereeuw R, Russel FGM. Mechanisms of renal anionic drug transport. *Eur J Pharmacol* 2008; **585**: 245–255.
149 Xu G, Bhatnagar V, Wen G, Hamilton BA, Eraly SA, Nigam SK. Analyses of coding region polymorphisms in apical and basolateral human organic anion transporter (OAT) genes [OAT1 (NKT), OAT2, OAT3, OAT4, URAT (RST)]. *Kidney Int* 2005; **68**: 1491–1499.
150 Ambudkar SV, Kimchi-Sarfaty C, Sauna ZE, Gottesman MM. P-glycoprotein: from genomics to mechanism. *Oncogene* 2003; **22**: 7468–7485.
151 Schwab M, Eichelbaum M, Fromm MF. Genetic polymorphisms of the human MDR1 drug transporter. *Annu Rev Pharmacol Toxicol* 2003; **43**: 285–307.
152 Shima Y, Teruya K, Ohta H. Association between intronic SNP in urate-anion exchanger gene, SLC22A12, and serum uric acid levels in Japanese. *Life Sci* 2006; **79**: 2234–2237.
153 Le J, Schiller DS. Aerosolized delivery of antifungal agents. *Curr Fungal Infect Rep* 2010; **4**: 96–102.
154 Ruhnke M, Yeates RA, Pfaff G, Sarnow E, Hartmann A, Trautmann M. Single-dose pharmacokinetics of fluconazole in patients with liver cirrhosis. *J Antimicrob Chemother* 1995; **35**: 641–647.
155 Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. *Antimicrob Agents Chemother* 2002; **46**: 2546–2553.
156 Shimuzu T, Ochiai H, Asell F, Yokono Y, Kikuchi Y, Nitta M *et al*. Bioinformatic research on inter-racial difference in drug metabolism II Analysis on relationship between enzyme activities of CYP2D6 and CYP 2C19 and their relevant genotypes. *Drug Metab Dispos* 2003; **18**: 71–78.
157 Kaneko A, Lum JK, Yaviong L, Takahashi N, Ishizaki T, Bertilsson L *et al*. High and variable frequencies of CYP2C19 mutations: medical consequences of poor drug metabolism in Vanuatu and other Pacific islands. *Pharmacogenetics* 1999; **9**: 581–590.
158 Kuti EL, Kuti JL. Pharmacokinetics, antifungal activity and clinical efficacy of anidulafungin in the treatment of fungal infections. *Expert Opin Drug Metab Toxicol* 2010; **6**: 1287–1300.
159 Ashley C, Currie A (eds) *The Renal Drug Handbook*, 2nd edn, Radcliffe Medical Press: Oxford, 2004.
160 Sakaeda T, Iwaki K, Kakumoto M, Nishikawa M, Niwa T, Jin JS *et al*. Effect of micafungin on cytochrome P450 3A4 and multidrug resistance protein 1 activities, and its comparison with azole antifungal drugs. *J Pharm Pharmacol* 2005; **57**: 759–764.
161 Wang EJ, Lew K, Casciano CN, Clement RP, Johnson WW. Interaction of common azole antifungals with P glycoprotein. *Antimicrob Agents Chemother* 2002; **46**: 160–165.
162 Yasuda K, Lan LB, Sanglard D, Furuya K, Schuetz JD, Schuetz EG. Interaction of cytochrome P450 3A inhibitors with P-glycoprotein. *J Pharmacol Exp Ther* 2002; **303**: 323–332.
163 Gupta A, Unadkat JD, Mao Q. Interactions of azole antifungal agents with the human breast cancer resistance protein (BCRP). *J Pharm Sci* 2007; **96**: 3226–3235.
164 Back DJ, Tjia JF. Comparative effects of the antimycotic drugs ketoconazole, fluconazole, itraconazole and terbinafine on the metabolism of cyclosporin by human liver microsomes. *Br J Clin Pharmacol* 1991; **32**: 624–626.
165 Mihara A, Mori T, Aisa Y, Yamazaki R, Iketani O, Tanigawara Y *et al*. Greater impact of oral fluconazole on drug interaction with intravenous calcineurin inhibitors as compared with intravenous fluconazole. *Eur J Clin Pharmacol* 2008; **64**: 89–91.
166 Balayssac D, Authier N, Cayre A, Coudore F. Does inhibition of P-glycoprotein lead to drug-drug interactions? *Toxicol Lett* 2005; **156**: 319–329.
167 Miyama T, Takanaga H, Matsuo H, Yamano K, Yamamoto K, Iga T *et al*. P-glycoprotein-mediated transport of itraconazole across the blood-brain barrier. *Antimicrob Agents Chemother* 1998; **42**: 1738–1744.
168 Lennernas H. Clinical pharmacokinetics of atorvastatin. *Clin Pharmacokinet* 2003; **42**: 1141–1160.
169 Hirano M, Maeda K, Shitara Y, Sugiyama Y. Drug-drug interaction between pitavastatin and various drugs via OATP1B1. *Drug Metab Dispos* 2006; **34**: 1229–1236.
170 Yoshikado T, Takada T, Yamamoto T, Yamaji H, Ito K, Santa T *et al*. Itraconazole-induced cholestasis: involvement of the inhibition of bile canalicular phospholipid translocator MDR3/ABCB4. *Mol Pharmacol* 2011; **79**: 241–250.
171 Buggia I, Zecca M, Alessandrino EP, Locatelli F, Rosti G, Bosi A *et al*. Itraconazole can increase systemic exposure to busulfan in patients given bone marrow transplantation. GITMO (Gruppo Italiano Trapianto di Midollo Osseo). *Anticancer Res* 1996; **16**: 2083–2088.
172 Varis T, Kivisto KT, Backman JT, Neuvonen PJ. The cytochrome P450 3A4 inhibitor itraconazole markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect. *Clin Pharmacol Ther* 2000; **68**: 487–494.
173 Olkkola KT, Backman JT, Neuvonen PJ. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994; **55**: 481–485.
174 Leather H, Boyette RM, Tian L, Wingard JR. Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; **12**: 325–334.
175 Lebrun-Vignes B, Archer VC, Diquet B, Levron JC, Chosidow O, Puech AJ *et al*. Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. *Br J Clin Pharmacol* 2001; **51**: 443–450.
176 Gillies J, Hung KA, Fitzsimons E, Soutar R. Severe vincristine toxicity in combination with itraconazole. *Clin Lab Haematol* 1998; **20**: 123–124.
177 Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. *Pharmacotherapy* 2006; **26**: 1730–1744.
178 Takara K, Tanigawara Y, Komada F, Nishiguchi K, Sakaeda T, Okumura K. Cellular pharmacokinetic aspects of reversal effects of itraconazole on P-glycoprotein-mediated resistance of anticancer drugs. *Biol Pharm Bull* 1999; **22**: 1355–1359.
179 Jeong S, Nguyen PD, Desta Z. Comprehensive in vitro analysis of voriconazole inhibition of eight cytochrome P450 (CYP) enzymes: major effect on CYPs 2B6, 2C9, 2C19, and 3A. *Antimicrob Agents Chemother* 2009; **53**: 541–551.
180 Mori T, Aisa Y, Kato J, Nakamura Y, Ikeda Y, Okamoto S. Drug interaction between voriconazole and calcineurin inhibitors in allogeneic hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2009; **44**: 371–374.
181 Groll AH, Kolve H, Ehlert K, Paulussen M, Vormoor J. Pharmacokinetic interaction between voriconazole and ciclo-

sporin A following allogeneic bone marrow transplantation. *J Antimicrob Chemother* 2004; **53**: 113–114.
182 Porter CC, Carver AE, Albano EA. Vincristine induced peripheral neuropathy potentiated by voriconazole in a patient with previously undiagnosed CMT1X. *Pediatr Blood Cancer* 2009; **52**: 298–300.
183 Saari TI, Laine K, Leino K, Valtonen M, Neuvonen PJ, Olkkola KT. Effect of voriconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Clin Pharmacol Ther* 2006; **79**: 362–370.
184 Schwiesow JN, Iseman MD, Peloquin CA. Concomitant use of voriconazole and rifabutin in a patient with multiple infections. *Pharmacotherapy* 2008; **28**: 1076–1080.
185 Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. *Eur J Pharm Sci* 2004; **21**: 645–653.
186 Sansone-Parsons A, Krishna G, Martinho M, Kantesaria B, Gelone S, Mant TG. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. *Pharmacotherapy* 2007; **27**: 825–834.
187 Stone JA, Holland SD, Wickersham PJ, Sterrett A, Schwartz M, Bonfiglio C *et al*. Single- and multiple-dose pharmacokinetics of caspofungin in healthy men. *Antimicrob Agents Chemother* 2002; **46**: 739–745.
188 Hebert MF, Townsend RW, Austin S, Balan G, Blough DK, Buell D *et al*. Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; **45**: 954–960.
189 Hebert MF, Blough DK, Townsend RW, Allison M, Buell D, Keirns J *et al*. Concomitant tacrolimus and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; **45**: 1018–1024.
190 FDA. Guidance for Industry. Bioanalytical Method Validation. 2001.
191 Honour JW. Development and validation of a quantitative assay based on tandem mass spectrometry. *Ann Clin Biochem* 2011; **48**: 97–111.
192 Denning DW, Tucker RM, Hanson LH, Stevens DA. Treatment of invasive aspergillosis with itraconazole. *Am J Med* 1989; **86**: 791–800.
193 Denning DW, Tucker RM, Hanson LH, Hamilton JR, Stevens DA. Itraconazole therapy for cryptococcal meningitis and cryptococcosis. *Arch Intern Med* 1989; **149**: 2301–2308.
194 Cartledge JD, Midgely J, Gazzard BG. Itraconazole solution: higher serum drug concentrations and better clinical response rates than the capsule formulation in acquired immunodeficiency syndrome patients with candidosis. *J Clin Pathol* 1997; **50**: 477–480.
195 Glasmacher A, Hahn C, Leutner C, Molitor E, Wardelmann E, Losem C *et al*. Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. *Mycoses* 1999; **42**: 443–451.
196 Jang SH, Colangelo PM, Gobburu JV. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. *Clin Pharmacol Ther* 2010; **88**: 115–119.
197 Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R *et al*. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007; **44**: 2–12.