Clinical Relevance of the Pharmacokinetic Interactions of Azole Antifungal Drugs with Other Coadministered Agents

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There are currently a number of licensed azole antifungal drugs; however; only 4 (namely, fluconazole, itraconazole, posaconazole, and voriconazole) are used frequently in a clinical setting for prophylaxis or treatment of systemic fungal infections. In this article, we review the pharmacokinetic interactions of these azole antifungal drugs with other coadministered agents. We describe these (2-way) interactions and the extent to which metabolic pathways and/or other supposed mechanisms are involved in these interactions. This article provides an overview of all published drug-drug interactions in humans (either healthy volunteers or patients), and on the basis of these findings, we have developed recommendations for managing the specific interactions.

Azole antifungal drugs exhibit a wide range and variety of drug-drug interactions. They are a substrate for and inhibitors of cytochrome P450 (CYP450) enzymes, as well as inhibitors of membrane transporters such as P-glycoprotein (P-gP). The inhibition or induction of CYP450 enzymes may alter the pharmacokinetic profile of the drugs involved and can thus affect both interacting agents. This type of interaction should be avoided whenever possible, because it can lead to either overdosing or underdosing of both drugs, leading to toxicity or to loss of efficacy, respectively. The risk of this type of pharmacokinetic interaction occurring between an azole antifungal drug and other drug classes can differ, depending on the individual drugs involved, even for drugs within the same class.

METHODS

A PubMed search of peer-reviewed journals and review articles was performed using the keywords "antifungal," "pharmacokinetics," "metabolism," "drug interactions," and the names of the individual antifungal drugs. Only drug-drug interactions studied clinically are detailed in this review, because the clinical importance of theoretical interactions cannot be properly assessed. The drug-drug interactions were tabulated according to risk category, with the most relevant category mentioned first. Within each category, the interacting agent is the primary determinant. Advice on how to cope with specific interactions has been provided as clearly as possible.

The prediction of metabolic drug-drug interactions in humans from in vitro investigations or studies in laboratory animals is not straightforward [1, 2]. Only human studies were considered for review, because, with respect to animals, substrate specificities and inhibitor potencies for the enzymes mediating drug biotransformation are not conserved between species.

PHARMACOKINETICS OF AZOLE ANTIFUNGAL DRUGS

Fluconazole. After oral administration, fluconazole is rapidly and fully (bioavailability >90%) absorbed, with a time to maximum absorption of 0.5–1.5 h after intake of the drug [3]. Tablets are bioequivalent to oral suspension and rectal suppositories [3, 4]. Fluconazole has a protein binding of 11%–12%, but this can increase up to 23% in patients with chronic renal failure [5]. The volume of distribution in adults is 0.56–0.82 L/kg [3, 6]. Elimination is primarily by renal excretion, with 80% of the drug being excreted unchanged and ~10% of

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the drug being metabolized [7, 8]. The elimination half-life for adults is ~30 h but is markedly reduced in children (15–25 h) [3]. For patients with renal failure, the maintenance dose has to be reduced by 50% [3]. For patients requiring hemodialysis, 1 full dose (100%) should be administered after every dialysis session [3].

Itraconazole. The oral formulation of itraconazole consists of capsules and an oral solution. Capsules have a less favorable pharmacokinetic profile, compared with the oral solution [9]. Systemic bioavailability of itraconazole oral solution is ~55% and is optimized under fasting conditions [10, 11]. Itraconazole is highly protein bound (>99%) [12] and penetrates extensively into human tissue [13], but it has limited penetration into the cerebrospinal fluid [14]. Itraconazole is extensively metabolized by the liver, predominantly by the CYP3A4 isoenzyme system, and is known to undergo enterohepatic recirculation [15]. Hydroxy-itraconazole is the major metabolite and shows an antifungal activity equal to that of the parent compound. Metabolites of itraconazole are excreted into the urine (40% of metabolites) and bile (55% of metabolites). Itraconazole is a substrate for and an inhibitor of CYP3A4 and an inhibitor of P-gP [10, 16].

Voriconazole. Voriconazole, given orally, is rapidly and almost fully absorbed (oral bioavailability >90%), with a maximum plasma concentration (C_{max}) being achieved ~2 h after administration under fasting conditions [17]. The volume of distribution of voriconazole is estimated to be ~4.6 L/kg, with a plasma protein binding of ~58% [18]. Voriconazole is extensively distributed into tissues and penetrates well into cerebrospinal fluid [19, 20] and into vitreous and aqueous humors [21–23]. The steady state plasma concentrations of voriconazole in healthy volunteers are reached after 5–7 days of treatment but can be reached after 24 h by giving a loading dose [24–26]. Voriconazole exhibits nonlinear pharmacokinetics, with a C_{max} and an area under the concentration-time curve (AUC) that increase more than proportionally with an increase in dose, possibly because of saturation of the hepatic metabolism of the drug. The major redundant metabolic pathway involves CYP2C19, with CYP2C9 and CYP3A4 being involved to a much lesser extent. The major metabolite of voriconazole possesses no antifungal activity. Voriconazole is an inhibitor of CYP2C9, CYP2C19, and CYP3A4. The drug's metabolites are primarily excreted in the urine [18]. The apparent serum half-life of voriconazole is ~6 h, but it can become longer with a higher dosage [27].

Posaconazole. Posaconazole is only available as an oral formulation. Like itraconazole, posaconazole is absorbed slowly, with a time to median maximum absorption of 5 h, and is also strongly bound to plasma proteins (>98%). The volume of distribution varies considerably, and steady state is reached after a period of 7–10 days [28–31]. Administration of 50–800 mg to healthy volunteers resulted in a linear pharmacokinetic profile [29], and doses of >800 mg showed no marked increase in total exposure. Administration of posaconazole in 2 or 4 divided daily doses leads to a 2-fold or 3-fold increase in exposure, respectively, compared with administration of 1 daily dose. Posaconazole is metabolized by a phase II reaction (uridine diphosphate–glucuronosyltransferase 1A4 enzyme system) and converted into a nonactive metabolite [32, 33]. Approximately 78% of the drug is recovered in fecal samples [33], and most of the metabolites are excreted into the urine with an elimination half-life of the parent compound of ~35 h (range, 20–66 h) [29]. Posaconazole is a substrate for P-gP in vitro.

MECHANISMS OF DRUG-DRUG INTERACTION

In general, pharmacokinetic interactions occur at the level of drug absorption, distribution, excretion, and metabolism, with the frequent involvement of the CYP450 metabolizing enzyme system and drug transporters such as P-gP (figure 1). The results of these interactions can be a decrease or an increase in exposure to both interacting drugs, which can in turn lead to reduced efficacy or increased toxicity, respectively. The mechanisms involved in pharmacokinetic drug-drug interactions are outlined in the following sections.

PHARMACOKINETIC INTERACTIONS

Drug Absorption

All 4 antifungal drugs (i.e., fluconazole, itraconazole, posaconazole, and voriconazole) discussed in this review can be given orally and require absorption through the mucous membranes of the gastrointestinal tract; therefore, a change in plasma concentrations can be the result of incomplete drug absorption. Drug absorption and, thus, the pharmacokinetic profile of a drug can be substantially influenced by gastric pH or by the presence of food.

Effect of food on the absorption of azoles. The pharmacokinetics and bioavailability of fluconazole are not affected by food. The mean bioavailability of itraconazole oral solution under steady state conditions was 43% higher for those who fasted than for those who did not [34]. Single and multiple oral doses of voriconazole with food lowered the bioavailability by ~22% and delayed absorption, compared with single and multiple oral doses of voriconazole without food [35]. Administration of voriconazole with a high-fat meal reduced the mean C_{max} and AUC by 34% and 24%, respectively [18]. For this reason, oral administration is recommended either 1 h before or 1 h after meals. Posaconazole absorption is strongly affected by the presence and composition of food. The mean AUC and C_{max} values increased by ~400% when posaconazole was administered with a high-fat meal, compared with when it was administered under fasting conditions [36]. The administration of posaconazole with a nonfat meal enhanced expo-

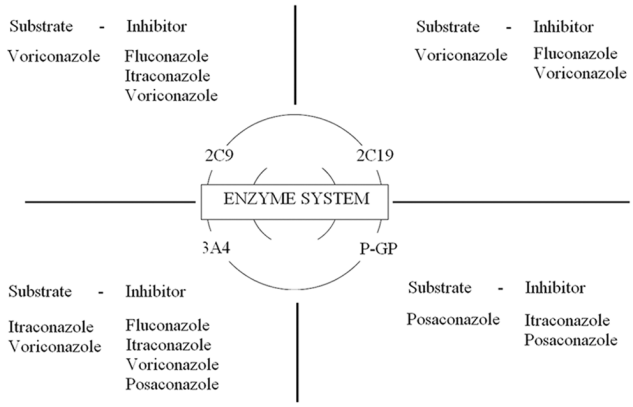

Figure 1. Involvement of cytochrome P450 enzymes and P-glycoprotein (P-gP) in the metabolism of azole antifungal drugs (adapted from Dr. Peter Donnelly).

sure, resulting in a 2.6-fold increase in the AUC and a 3.0-fold increase in the C_{max}, relative to the administration of posaconazole under fasting conditions [37, 38]. The coadministration of posaconazole with a nutritional supplement resulted in a 3.4-fold increase in the C_{max} and a 6-fold increase in the AUC, relative to the administration of posaconazole under fasting conditions [39]. The daily dose of posaconazole should be divided for malnourished patients (e.g., 200 mg 4 times a day).

Effect of gastric pH and acid-reducing agents on the absorption of azoles. The absorption of fluconazole is not affected by drugs that increase gastric pH [40]. The concomitant administration of itraconazole and proton pump inhibitors (e.g., omeprazole) or H_2 receptor antagonists (e.g., famotidine and ranitidine) leads to impaired absorption of itraconazole, resulting in a decrease in exposure [10].

The absorption of voriconazole is not markedly influenced by antacids or proton pump inhibitors, although the mean C_{max} and AUC values of voriconazole are increased by 15% and 41% when coadministered with omeprazole, because of the inhibition of plasma clearance of voriconazole [41]. The C_{max} and AUC values of posaconazole were both reduced by 39% when coadministered with cimetidine (400 mg twice daily), possibly as a result of decreased gastric acid production. The effects of proton pump inhibitors (e.g., esomeprazole) that may suppress gastric acidity for several hours have only been presented in abstract form [36]. The concomitant administration of posaconazole with esomeprazole resulted in a 33% decrease in posaconazole exposure [28].

Not only the gastric pH but also the integrity of the gastrointestinal tract may be important factors for the absorption of antifungal drugs. For instance, posaconazole absorption appeared to be reduced in patients with grade 1 or grade 2 mucositis, compared with patients without mucositis (AUC for 400 mg of posaconazole twice daily, 4.54 vs. 8.85 mg $\times$ h/L) [42].

Metabolism

Drug metabolism mainly occurs in the liver, where 2 types of reactions occur. Most drugs are metabolized by phase I reactions that involve oxidation, reduction, and hydrolysis principally involving the CYP450 enzymes. In contrast, phase II reactions are not mediated by CYP enzymes but involve the conjugation of the drugs. Drugs can be substrates, inducers, or inhibitors. Substrates are moieties that undergo metabolism by $\geqslant$1 enzyme. Enzyme induction can lead to either increased drug exposure (in the case of a prodrug) and decreased drug exposure, with subsequent decreased effect. It may take from up to a few days to 2–3 weeks for enzyme induction to reach its full extent. Enzyme inhibition, on the other hand, is instantaneous and is dependent on the dose of the drug.

Effect of Azole Antifungal Drugs on Comedication

All azoles inhibit the CYP3A4 isoenzyme (figure 1). In humans, CYP3A comprises the largest fraction of the total CYP content and is responsible for the metabolism of a broad range of drugs. Furthermore, CYP3A4 is involved in presystemic metabolism in the gastrointestinal tract, influencing the absorption of CYP3A substrates. The inhibitory potential of each of the azole antifungal drugs varies greatly: itraconazole and posaconazole are more-potent inhibitors of CYP3A4 than are fluconazole or voriconazole. In addition to CYP3A4, fluconazole and voriconazole are also strong noncompetitive or mixed-type inhibitors of CYP2C9 and CYP2C19 [27, 43, 44]. The clinical relevance of the pharmacokinetic interactions depends on the CYP isoform that metabolizes the coadministered drug and on the potency of the antifungal agent as an inhibitor of that isoform.

Table 1. Interaction of azole antifungal drugs with coadministered agents.

Category, reference(s)	Coadministered agent(s)	Antifungal agent	Type of study	Type of participants	No. of participants	Interaction mechanism	Effect(s) of interaction	Recommendation
Category X: avoid combination[a]								
[57]	Antacids	ITZ	Open-label randomized, crossover	Healthy volunteers	12	Stomach pH	ITZ AUC decreased by >50%; C_{max} decreased by ⩽50%	Avoid combination
[58]	Carbamazepine and/or phenobarbital	ITZ	Case report	Patients	3	Induction of CYP3A4	ITZ C_{min} decreased by ⩽50%	Avoid combination
[28]	Cimetidine	PSZ	Not available	Not available	Not available	Unknown	PSZ AUC and C_{max} decreased by ⩽50%	Avoid combination; if combined, initiate TDM of PSZ and increase dose if necessary
[59]	Didanosine chewable tablet	ITZ	Open-label, randomized, crossover	Healthy volunteers	7	Unknown	ITZ AUC and C_{max} decreased by >50%	Use enteric-coated capsules (Videx EC); do not use chewable tablets (these contain antacids)
[60]	Fluticasone	ITZ	Open-label, nonrandomized, parallel	Lung transplant recipients	20	Inhibition of CYP3A4	Fluticasone C_{ss} increased by >100%	Avoid combination; monitor adverse effects
[61]	Grapefruit juice	ITZ tablet	Open-label, randomized, crossover	Healthy volunteers	11	Inhibition of intestinal CYP3A4	ITZ AUC and C_{max} decreased by ⩽50%; hITZ AUC and C_{max} decreased by ⩽50%	Avoid combination; use ITZ oral solution
[62]	Lovastatin	ITZ	Double-blind, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	Lovastin AUC and C_{max} increased by >100%	Avoid combination
[63]	Lovastatin	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Lovastin AUC and C_{max} increased by >100%	Avoid combination
[64]	Omeprazole	ITZ	Open-label, nonrandomized	Healthy volunteers	11	Stomach pH increase	ITZ C_{max} and AUC decreased by >50%	Avoid combination with ITZ capsules; use oral solution ITZ
[65]	Phenytoin	ITZ	Open-label, randomized, parallel	Healthy volunteers	28	Induction of CYP3A4	ITZ AUC and C_{max} decreased by >50%; phenytoin AUC increased by ⩽100%	Avoid combination; TDM of ITZ
[66]	Phenytoin	PSZ	Open-label, randomized, parallel	Healthy volunteers	36	Unknown	PSZ AUC decreased by >50% and C_{max} decreased by ⩽50%	Avoid combination; if no alternative, increase dose of PSZ and initiate TDM of PSZ; monitor for toxicity of phenytoin, TDM of phenytoin
[67]	Rifabutin	PSZ	Open-label, nonrandomized, parallel	Healthy volunteers	24	Unknown	PSZ AUC and C_{max} decreased by ⩽50%; rifabutin AUC and C_{max} increased by ⩽100%	Avoid combination; otherwise increase PSZ dose, TDM of PSZ; monitor for toxicity of rifabutin
[68]	Rifampin	ITZ	Open-label, nonrandomized, parallel, crossover	Combination of healthy volunteers and patients with AIDS	9	Induction of CYP450	ITZ AUC and C_{max}decreased by >50%	Avoid combination
[28]	Sirolimus	PSZ	Healthy volunteers	Not available	Not available	Unknown	Sirolimus AUC and C_{max} increased by >100%	Avoid combination
[69]	Sirolimus	VRZ	Retrospective	Patients	11	Inhibition of CYP3A4	Sirolimus AUC increased by >100%	Avoid combination
[70]	St. John's wort	VRZ	Controlled, open-label	Healthy volunteers	16	Induction of CYP450	Short-term increase in exposure followed by a reduced exposure of VRZ	Avoid combination
[71]	Terfenadine	ITZ	Open-label, nonrandomized, crossover	Healthy volunteers	6	Inhibition of CYP3A4	Terfenadine AUC increased by ⩽100%; QT prolongation	Avoid combination
[72]	Triazolam	ITZ	Open-label, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Triazolam AUC increased by >100% and C_{max} increased by ⩽100%	Avoid combination; monitor for toxicity of triazolam
[73]	Triazolam	ITZ	Double-blind, randomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4	Triazolam AUC and C_{max} increased by >100%	Avoid combination; monitor for toxicity of triazolam
[74–82]	Vincristine	ITZ	Case reports	Patients	Multiple patients in multiple reports	Inhibition of CYP3A4, P-gP	Unknown	Avoid combination; monitor for toxicity of vincristine

Category D: consider therapy modification[b]								
[83]	Alfentanil	FLZ	Double-blind, randomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4	Alfentanil AUC increased by ⩽100%	Monitor for toxicity of alfentanyl and adjust dose of alfentanyl if necessary
[84]	Alfentanil	VRZ	Open-label, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	Alfentanil AUC increased by >100%	Monitor for toxicity of alfentanyl and adjust dose of alfentanil if necessary
[85]	Amitriptyline	FLZ	Case report	Patients with AIDS and ESRD	3	Inhibition of CYP2C9	Amitriptyline AUC increased by ⩽100%	Monitor for toxicity of amitryptiline; TDM of amitryptiline
[28]	Atazanavir (either with or without ritonavir)	PSZ	Not available	Patients	Not available	Unknown	Atazanavir AUC and C_{max} increased by >100%; atazanavir plus ritonavir AUC increased by >100% and C_{max} increased by ⩽100%	Monitor for toxicity of atazanavir, TDM of atazanavir
[86]	Atorvastatin	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Atorvastatin AUC and active metabolites increased by >100% and C_{max} increased by ⩽100%	Monitor for toxicity of atorvastatin and adjust dose if necessary; upon initiation of therapy, start with low dose of atorvastatin
[87]	Budesonide	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Budesonide AUC increased by >100% and C_{max} increased by ⩽100%	Increased risk of adverse effects
[88]	Budesonide	ITZ	Open-label, nonrandomized, with retrospective matched control subjects	Patients with CF and CGD	67	Inhibition of CYP3A4	Not available	Monitor adrenal function
[89]	Cabergoline	ITZ	Case reports	Patients with PD	2	Inhibition of CYP3A4	Cabergoline C_{ss} increased by >100%	Reduce dose of cabergoline
[90]	Celiprolol	ITZ	Open-label, randomized, crossover	Healthy volunteers	12	P-gP	Celiprolol AUC and C_{max} increased by ⩽100%	Monitor for toxicity of celiprolol and reduce dose if necessary
[91]	CsA	FLZ	Double-blind, randomized	Renal transplant recipients	16	Inhibition of CYP3A4	CsA AUC increased by ⩽100%	Monitor for toxicity of CsA and adjust dose if necessary; TDM of CsA
[92]	CsA	FLZ	Open-label, crossover	Renal transplant recipients	6	Inhibition of CYP3A4	CsA AUC increased by >100% and C_{max} increased by ⩽100%	Monitor for toxicity of CsA and adjust dose if necessary; TDM of CsA
[93]	CsA	FLZ	Open-label, nonrandomized	Patients	6	Inhibition of gut metabolism	CsA AUC and C_{max} increased by ⩽100%	Monitor for toxicity of CsA and adjust dose if necessary; TDM of CsA
[94]	CsA	ITZ	Open-label, nonrandomized	Renal transplant recipients	8	Inhibition of CYP3A4	CsA AUC and C_{max} increased by ⩽100%	Monitor for toxicity of CsA; TDM of CsA; upon initiation of CsA, start with a 50% reduced dose of CsA; a dose reduction of 50% of CsA upon initiation of azole seems warranted
[95]	CsA	ITZ	Open-label, nonrandomized, crossover	SCT recipients	8	Inhibition of CYP3A4	CsA C_{ss} increased by ⩽100%	Monitor for toxicity of CsA; TDM of CsA; upon initiation of CsA, start with a 50% reduced dose of CsA; a dose reduction of 50% of CsA upon initiation of azole seems warranted
[96]	CsA	PSZ	Open-label, nonrandomized	Heart transplant recipients	4	Inhibition of CYP3A4	CsA increased by ⩽100%	Monitor for toxicity of CsA; TDM of CsA; upon initiation of CsA, start with a 75% reduced dose of CsA; a dose reduction of 75% of CsA upon initiation of azole seems warranted
[97]	CsA	VRZ	Randomized, placebo-controlled, double-blind, crossover	Renal transplant recipients	7	Inhibition of CYP3A4	CsA AUC increased by >100%	Monitor for toxicity of CsA; TDM of CsA; upon initiation of CsA, start with a 66% reduced dose of CsA; a dose reduction of 66% of CsA upon initiation of azole seems warranted
[98]	Cimetidine	ITZ	Open-label, nonrandomized, crossover	Healthy volunteers	8	P-gP	Cimetidine AUC increased by ⩽100%	Monitor for toxicity of cimetidine
[99]	Diclofenac	VRZ	2-way, open-label, crossover	Healthy volunteers	10	Inhibition of CYP2C9, CYP3A4, and CYP2C19	Diclofenac AUC and C_{max} increased by >100%	Clinical relevance unknown

[100]	Digoxin	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	P-gP	Digoxin AUC and C_{max} increased by ⩽100%	Monitor digoxin plasma level
[28]	Efavirenz	PSZ	Not available	Not available	Not available	Unknown	PSZ AUC and C_{max} decreased by ⩽50%	TDM of PSZ, increase dose of PSZ if necessary
[101]	Efavirenz	VRZ	Randomized, placebo-controlled	Healthy volunteers	34	Induction of CYP2C19 and CYP2C9 by efavirenz; inhibition of CYP3A4 by VRZ	Efavirenz AUC and C_{max} increased by ⩽100%; VRZ AUC and C_{max} decreased by >50%	Use 300 mg efavirenz once daily, use 400 mg VRZ twice daily; TDM of efavirenz and VRZ
[102]	Efavirenz	VRZ	Open-label, nonrandomized	Healthy volunteers	16	Induction of CYP2C19 and CYP2C9 by efavirenz; inhibition of CYP3A4 by VRZ	Efavirenz AUC and C_{max} increased by ⩽100%; VRZ AUC decreased by >50% and C_{max} decreased by ⩽50%	Use 300 mg efavirenz once daily, use 400 mg VRZ twice daily; TDM of efavirenz and VRZ
[103]	Ethinyl estradiol and norethindrone	VRZ	Open-label, nonrandomized	Healthy volunteers	16	Inhibition of CYP2C19 by ethinyl estradiol; inhibition of CYP3A4 by VRZ	VRZ AUC and C_{max} increased by ⩽100%; ethinyl estradiol AUC and C_{max} increased by ⩽100%; norethindrone AUC and C_{max} increased by ⩽100%	Monitor for toxicity of voriconazole and oral contraceptive
[104]	Felodipine	ITZ	Double-blind, randomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4	Felodipine C_{max} and AUC increased by >100%	Monitor for felodipine toxicity, adjust dose of felodipine if necessary
[105]	Fluvastatin	FLZ	Double-blind, randomized, crossover	Healthy volunteers	12	Inhibition of CYP2C9	Fluvastatin AUC and C_{max} increased by ⩽100%	Monitor for toxicity of fluvastatin and adjust dose if necessary; upon initiation of therapy, start with low dose of fluvastatin
[106]	Glimepiride	FLZ	Double-blind, randomized, crossover	Healthy volunteers	12	Inhibition of CYP2C9	Glimepiride AUC increased by >100% and C_{max} increased by ⩽100%	Monitor for glimepiride toxicity and adjust dose if necessary
[107]	Methadone	VRZ	Randomized, placebo-controlled, double-blind, parallel	Patients receiving methadone therapy	23	Inhibition of CYP3A4, CYP2C9, and/or CYP2C19	Methadone AUC increased by >100%	Monitor for toxicity of methadone and adjust dose if necessary
[108]	MDZ	FLZ	Open-label, randomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4	MDZ AUC increased by >100% and C_{max} increased by ⩽100%	Monitor for toxicity of MDZ and adjust dose if necessary
[109]	MDZ	FLZ	Open-label, parallel	ICU patients	10	Inhibition of CYP3A4	MDZ AUC increased by >100%	Monitor for toxicity of MDZ and adjust dose if necessary
[110]	MDZ	FLZ	Double-blind, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	MDZ AUC increased by >100% and C_{max} increased by ⩽100%	Monitor for toxicity of MDZ and adjust dose if necessary
[111]	MDZ	FLZ	Open-label, parallel	Healthy volunteers		Inhibition of CYP3A4	MDZ AUC increased by ⩽100%	Monitor for toxicity of MDZ and adjust dose if necessary
[112]	MDZ	ITZ	Double-blind, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	MDZ AUC and C_{max} increased by >100%	Monitor for toxicity of MDZ and adjust dose if necessary
[113]	MDZ	ITZ	Open-label, nonrandomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4	MDZ AUC and C_{max} increased by >100%	Monitor for toxicity of MDZ and adjust dose if necessary
[114]	MDZ	ITZ	Double-blind, randomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4	MDZ AUC and C_{max} increased by >100%	Monitor for toxicity of MDZ and adjust dose if necessary
[110]	MDZ	ITZ	Double-blind, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	MDZ AUC and C_{max} increased by >100%	Monitor for toxicity of MDZ and adjust dose if necessary
[115]	MDZ	PSZ	Open-label, randomized, crossover	Healthy volunteers	13	Inhibition of CYP3A4	MDZ AUC increased by ⩽100%	Monitor for toxicity of MDZ and adjust dose if necessary
[116]	MDZ	VRZ	Open-label, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	MDZ AUC and C_{max} increased by >100%	Monitor for toxicity of MDZ and adjust dose if necessary
[117]	Nelfinavir	FLZ	Case report	HIV-infected patients	3	Inhibition of CYP2C19 and CYP3A4	Nelfinavir AUC increased by ⩽100%	TDM of nelfinavir and adjust dose if necessary, if boosted with ritonavir
[118]	Nevirapine	ITZ	Open-label, randomized, crossover	Healthy volunteers	12	Induction of CYP3A4 by nevirapine	ITZ C_{max} decreased by ⩽50% and AUC decreased by >50%	TDM of ITZ and increase dose of ITZ
[119]	Omeprazole	FLZ	Open-label, nonrandomized, crossover	Healthy volunteers	18	Inhibition of CYP2C19 and CYP3A4	Omeprazole AUC increased by >100% and C_{max} increased by ⩽100%	Monitor for toxicity of omeprazole and adjust dose if necessary; upon initiation of therapy, start with low dose of omeprazole

[41]	Omeprazole	VRZ	Open-label, randomized, placebo-controlled, 2-way crossover	Healthy volunteers	18	Inhibition of CYP2C19	VRZ AUC increased by ⩽100%; omeprazole AUC increased by >100% and C_{max} increased by ⩽100%	No clinically relevant effect on VRZ; monitor for toxicity of omeprazole and adjust dose if necessary; upon initiation of therapy, start with low dose of omeprazole
[120]	Phenytoin	FLZ	Open-label, randomized, parallel	Healthy volunteers	20	Inhibition of CYP2C9	Phenytoin AUC increased by ⩽100%	Monitor for toxicity of phenytoin and adjust dose if necessary; TDM of phenytoin
[45]	Phenytoin	VRZ	Study A: open-label; study B: double-blind, randomized	Healthy volunteers	Study A: 21; study B: 15	Induction of CYP2C19 and CYP2C9 by phenytoin; inhibition of CYP2C9 by VRZ	VRZ AUC and C_{max} decreased by >50%; phenytoin AUC and C_{max} increased by >100%	Increase VRZ maintenance dose to 400 mg twice daily, TDM of VRZ; monitor for toxicity of phenytoin, TDM of phenytoin
[121]	Ritonavir	VRZ	Study A: randomized, double-blind, placebo-controlled, parallel; study B: randomized	Healthy volunteers	Study A: 34; study B: 17	Induction of CYP2C19 and CYP2C9	VRZ AUC and C_{max} decreased by >50%	Consider alternative therapy; TDM of VRZ
[122]	Ritonavir	VRZ	Randomized, placebo-controlled, crossover	Healthy volunteers	20	Inhibition of CYP3A4	VRZ AUC and C_{max} increased by ⩽100%	Consider alternative therapy; TDM of VRZ
[123]	Saquinavir	ITZ	Open-label, randomized, parallel	HIV-infected patients	17	Inhibition of CYP3A4 and P-gP	Saquinavir AUC increased by ⩽100%	Monitor for toxicity of saquinavir and adjust dose if necessary; TDM of saquinavir
[124]	Simvastatine	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Simvastatin AUC and C_{max} increased by >100%	Monitor for toxicity of simvastatin and adjust dose if necessary; upon initiation of therapy, start with low dose of simvastatin
[93]	TAC	FLZ	Open-label, nonrandomized	Patients	15	Inhibition of gut metabolism	TAC AUC and C_{max} increased by ⩽100%	Monitor for toxicity of TAC; TDM of TAC; upon initiation of TAC, start with a 50% reduced dose of TAC; a dose reduction of 50% of TAC upon initiation of azole seems warranted
[125]	TAC	FLZ	Open-label, nonrandomized	Kidney, liver, and heart transplant recipients	16	Inhibition of CYP3A4	TAC C_{min} increased by >100%	Monitor for toxicity of TAC; TDM of TAC; upon initiation of TAC, start with a 50% reduced dose of TAC; a dose reduction of 50% of TAC upon initiation of azole seems warranted
[95]	TAC	ITZ	Open-label, nonrandomized, crossover	HSCT recipients	9	Inhibition of CYP3A4	TAC C_{ss} increased by ⩽100%	Monitor for toxicity of TAC; TDM of TAC; upon initiation of TAC, start with a 50% reduced dose of TAC; a dose reduction of 50% of TAC upon initiation of azole seems warranted
[126]	TAC	ITZ	Retrospective	Lung transplant recipients	40	Inhibition of CYP3A4	TAC C_{min} increased by >100%	Monitor for toxicity of TAC; TDM of TAC; upon initiation of TAC, start with a 50% reduced dose of TAC; a dose reduction of 50% of TAC upon initiation of azole seems warranted
[96]	TAC	PSZ	Open-label, nonrandomized	Healthy volunteers	34	Inhibition of CYP3A4	TAC AUC and C_{max} increased by >100%	Monitor for toxicity of TAC; TDM of TAC; upon initiation of TAC, start with a 50% reduced dose of TAC; a dose reduction of 50% of TAC upon initiation of azole seems warranted
[127]	Zolpidem	VRZ	Open-label, randomized, 2-phase, crossover	Healthy volunteers	10	Inhibition of CYP2C9 and CYP3A4	Zolpidem AUC increased by ⩽100%	Monitor for toxicity of zolpidem and adjust dose if necessary
Category C: monitor therapy[c]								
[128]	Alprazolam	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Alprazolam AUC increased by ⩽100%	Monitor for toxicity of alprazolam
[129]	Bromperidol	ITZ	Open-label, nonrandomized, crossover	Healthy volunteers	8	Inhibition of CYP3A4	Bromperidol C_{ss} increased by ⩽100%	Monitor for adverse effects of bromperidol

[130]	Cimetidine	VRZ	Open-label, randomized, placebo-controlled, crossover	Healthy volunteers	12	Inhibition of CYP450 by cimetidine	VRZ AUC and C_{max} increased by ⩽100%	Monitor for toxicity of VRZ
[131]	Clarithromycin	ITZ	Case report	Patients with MAI	3	Inhibition of CYP3A4	Clarithromycin AUC increased by ⩽100%	Clinical relevance unknown; monitor for toxicity of clarithromycin
[132]	Cyclophosphamide	FLZ	Open-label, randomized,	SCT recipients	104	Inhibition of CYP2C9	Alternative metabolic pathway	Monitor for toxicity of cyclophosphamide
[132]	Cyclophosphamide	ITZ	Open-label, randomized	SCT recipients	105	Inhibition of CYP3A4	AUC of metabolites increased by ⩽100%	Monitor for toxicity of cyclophosphamide
[133]	Dexamethasone	ITZ	Double-blind, randomized, crossover	Healthy volunteers	8	Inhibition of CYP3A4	Dexamethasone AUC increased by >100% and C_{max} increased by ⩽100%	Monitor for toxicity of dexamethasone
[134]	Diazepam	FLZ	Open-label, randomized, crossover	Healthy volunteers	12	Inhibition of CYP2C19 and CYP3A4	Diazepam AUC increased by ⩽100%	Monitor for toxicity of diazepam and adjust dose if necessary
[135]	Diazepam	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Diazepam AUC increased by ⩽100%	Monitor for toxicity of diazepam
[134]	Diazepam	VRZ	Open-label, randomized, crossover	Healthy volunteers	12	Inhibition of CYP2C19 and CYP3A4	Diazepam AUC increased by ⩽100%	Monitor for toxicity of diazepam and adjust dose if necessary
[136]	Etizolam	ITZ	Double-blind, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	Etizolam AUC increased by ⩽100%	Monitor for toxicity of etizolam
[137]	Fentanyl	FLZ	Open-label, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	Fentanyl AUC increased by ⩽100%	Monitor for toxicity of fentanyl
[138]	Fentanyl	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	No effect	No clinical relevance, no action
[137]	Fentanyl	VRZ	Open-label, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	Fentanyl AUC increased by ⩽100%	Monitor for toxicity of fentanyl
[139]	Haloperidol	ITZ	Double-blind, randomized, crossover	Healthy volunteers	19	Inhibition of CYP3A4	Haloperidol AUC and C_{max} increased by ⩽100%	Monitor for toxicity of haloperidol
[140]	Ibuprofen	FLZ	Open-label, randomized, parallel	Healthy volunteers	12	Inhibition of CYP2C9	Ibuprofen AUC increased by ⩽100%	Monitor for toxicity of ibuprofen
[140]	Ibuprofen	VRZ	Open-label, randomized, crossover	Healthy volunteers	12	Inhibition of CYP2C9	Ibuprofen AUC increased by ⩽100%	Monitor for toxicity of ibuprofen
[141]	Loperamide	ITZ	Open-label, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4, P-gP	Loperamide AUC and C_{max} increased by >100%	Monitor for toxicity of loperamide
[142]	Losartan	FLZ	Open-lable, randomized, parallel	Healthy volunteers	16	Inhibition of CYP2C9 and CYP3A4	Losartan AUC and C_{max} increased by ⩽100%	Effect unclear; monitor for toxicity of losartan
[143]	Losartan	FLZ	Double-blind, randomized, crossover	Healthy volunteers	11	Inhibition of CYP2C9	Losartan AUC increased by ⩽100%; active metabolite AUC decreased by ⩽50%	Effect unclear; monitor for toxicity of losartan
[144]	Methylprednisolone	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Methylprednisolone AUC increased by >100%	Monitor for toxicity of methylprednisolone
[145]	Perispirone	ITZ	Open-label, nonrandomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4	Perispirone AUC and C_{max} increased by >100%	Monitor for toxicity of perispirone
[146]	Quinidine	ITZ	Open-label, nonrandomized, crossover	Healthy volunteers	6	Inhibition of CYP3A4, P-gP	Quinidine C_{max} increased by ⩽100%	Monitor for toxicity of quinidine
[147]	Quinidine	ITZ	Double-blind, randomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4, P-gP	Quinidine AUC increased by >100% and C_{max} increased by ⩽100%	Monitor for toxicity of quinidine
[148]	Repaglinide	ITZ	Open-label, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	Repaglinide AUC and C_{max} increased by ⩽100%	Monitor for toxicity of repaglinide
[149]	Rifabutin	FLZ	Open-label, nonrandomized, crossover	HIV-infected patients	12	Inhibition of CYP3A4	Rifabutin AUC increased by ⩽100% and rifabutin metabolite AUC increased by >100%	Monitor for toxicity of rifabutin
[150]	Rifabutin	FLZ	Open-label, randomized	HIV-infected patients	10	Inhibition of CYP3A4	Rifabutin AUC and C_{max} increased by ⩽100%	Monitor for toxicity of rifabutin
[151]	Rifampin	FLZ	Open-label, nonrandomized	Patients with AIDS	11	Induction of CYP450	No effect	Monitor efficacy of FLZ; TDM of FLZ
[152]	Rifampin	FLZ	Open-label, parallel	Patients with AIDS	24	Induction of CYP450	FLZ AUC and C_{max} decreased by ⩽50%	Monitor efficacy of FLZ; TDM of FLZ

[153]	Rifampin	FLZ	Case series, parallel controlled	ICU patients	2	Induction of CYP450	FLZ AUC decreased by ⩽50%	Monitor efficacy of FLZ; TDM of FLZ
[154]	Risperidone	ITZ	Open-label, nonrandomized, crossover	Schizophrenic patients	19	Inhibition of CYP3A4	Risperidone C_{ss} increased by ⩽100%	Monitor for toxicity of risperidone
[155]	Ropivacaine	ITZ	Double-blind, randomized, crossover	Healthy volunteers	8	Inhibition of CYP3A4	Ropivacaine AUC increased by ⩽100% and C_{max} decreased by ⩽50%	Monitor for toxicity of ropivacaine
[156, 157]	Triazolam	FLZ	Double-blind, randomized, crossover	Healthy volunteers		Inhibition of CYP3A4	Triazolam AUC and C_{max} increased by ⩽100%	Monitor for toxicity of triazolam
[158]	Venlafaxin	VRZ	Unknown	Healthy volunteers	12	Inhibition of CYP3A4, CYP2C9, and CYP2C19	Venlafaxin AUC increased by ⩽100%	Monitor for toxicity of venlafaxin
[43]	Warfarin	FLZ	Open-label, nonrandomized	Healthy volunteers	6	Inhibition of CYP3A4 and CYP2C9	Warfarin AUC increased by ⩽100%	Monitor for toxicity of warfarin
[159]	Warfarin	VRZ	Double-blind, placebo-controlled, crossover	Healthy volunteers	17	Inhibition of CYP2C9	Warfarin-induced increase of AUC and maximum of prothrombin time	Monitor for toxicity of warfarin
Category B: no action needed[d]								
[160]	Aripiprazole	ITZ	Open-label, nonrandomized, crossover	Healthy volunteers	24	Inhibition of CYP3A4	Aripiprazole AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[161]	Atenolol	ITZ	Open-label, randomized, crossover	Healthy volunteers	10	P-gP	No effect	No clinical relevance, no action
[162]	Azithromycin	VRZ	Open-label, randomized, parallel	Healthy volunteers	30	Unknown	VRZ AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[163]	Bupivacaine	ITZ	Double-blind, randomized, crossover	Healthy volunteers	7	Unknown	Bupivacaine C_{ss} increased by ⩽100%	No clinical relevance, no action
[164]	Busulfan	FLZ	Open-label, nonrandomized, parallel	SCT recipients	52	Unknown	Busulfan AUC increased by ⩽100%	No clinical relevance, no action
[165]	Cotrimoxazole	FLZ	Open-label, randomized, parallel	HIV-infected patients	Part A: 9; part B: 12	Inhibition of CYP2C9	AUC of hydroxylamine decreased by ⩽50%	Clinical relevance unknown
[166]	Didanosine	ITZ	Open-label, randomized, crossover	Healthy volunteers	27	pH	No effect	Use enteric-coated capsules (Videx EC); do not use chewable tablets (these contain antacids)
[162]	Erythromycin	VRZ	Open-label, randomized, parallel	Healthy volunteers	30	Inhibition of CYP3A by erythromycin	VRZ C_{max} increased by ⩽100%	No clinical relevance, no action
[167]	Ethinyl estradiol	FLZ	Open-label, randomized, crossover	Healthy volunteers	20	Inhibition of CYP3A4	Ethinyl estradiol AUC and C_{max} increased by ⩽100%	Clinical relevance unknown
[168]	Ethinyl estradiol and norethindrone	FLZ	Double-blind, randomized, crossover	Healthy volunteers	21	Unknown	Ethinyl estradiol AUC and C_{max} increased by ⩽100%; norethindrone AUC and C_{max} increased by ⩽100%	No threat of contraceptive failure, no action
[169]	Everolimus	FLZ	Case report	Renal transplant recipients	16	Inhibition of CYP3A4	No effect	No clinical relevance, no action
[170]	Fexofenadine	ITZ	Open-label, randomized, crossover	Healthy volunteers	10	P-gP	Fexofenadine AUC and C_{max} increased by >100%	No clinical relevance, no action
[171]	Fexofenadine	ITZ	Open-label, nonrandomized	Healthy volunteers	14	P-gP (*MDR1*-G2677T or -C3435T haplotype)	Fexofenadine AUC increased by >100%	No clinical relevance, no action
[172]	Fexofenadine	ITZ	Open-label, randomized, crossover	Healthy volunteers	11	P-gP	Fexofenadine AUC and C_{max} increased by >100%	No clinical relevance, no action
[173]	Gefitinib	ITZ	Open-label, randomized, crossover	Healthy volunteers	48	Inhibition of CYP3A4	Gefitinib AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[174]	Grapefruit juice	ITZ oral solution	Open-label, randomized, crossover	Healthy volunteers	20	Inhibition of intestinal CYP3A4	ITZ AUC increased by ⩽100%	No clinical relevance, no action
[175]	Lasofoxifene	FLZ	Open-label, randomized, parallel	Healthy volunteers	45	Inhibition of CYP2C9	No effect	No action

[176]	Intravenous lignocaine	ITZ	Double-blind, randomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4	Lignocaine AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[177]	Oral lignocaine	ITZ	Double-blind, randomized, crossover	Healthy volunteers	9	Inhibition of CYP3A4	Lignocaine AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[178]	Lumiracoxib	FLZ	Open-label, randomized, crossover	Healthy volunteers	13	Inhibition of CYP2C9	Lumiracoxib AUC increased by ⩽100%	No clinical relevance, no action
[107]	Methadone	FLZ	Double-blind, randomized	Patients receiving methadone therapy	25	Inhibition of CYP3A4	Methadone AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[179]	Omeprazole	ITZ	Open-label, randomized, crossover	Healthy volunteers	15	Stomach pH increase	No effect on ITZ	No action in case of ITZ oral solution
[180]	Oxybutinin	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Oxybutinin AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[181]	Prednisolone	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Prednisolone AUC increased by ⩽100%	No clinical relevance, no action
[130]	Ranitidine	VRZ	Open-label, randomized, placebo-controlled, crossover	Healthy volunteers	12	Inhibition of CYP450	VRZ AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[182]	Ritonavir	FLZ	Open-label, randomized, crossover	Healthy volunteers	8	Inhibition of CYP3A4	Ritonavir AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[183]	Ritonavir	FLZ	Open-label, parallel	HIV-infected patients	3	Inhibition of CYP3A4	No effect	No clinical relevance, no action
[184]	Rosuvastatin	FLZ	Double-blind, randomized, crossover	Healthy volunteers	14	Inhibition of CYP2C9 and CYP2C19	Rosuvastatin AUC increased by ⩽100%	No clinical relevance, no action
[185]	Rosuvastatin	ITZ	Double-blind, randomized, crossover	Healthy volunteers	Trial A: 12; trial B: 14	Inhibition of CYP3A4	Rosuvastatin AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[183]	Saquinavir	FLZ	Open-label, parallel	HIV-infected patients	5	Inhibition of CYP3A4	Saquinavir AUC and C_{max} increased by ⩽100%	No clinical relevance, no action
[186]	Temazepam	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Unknown	Temazepam AUC increased by ⩽100%	No clinical relevance, no action
[187]	Terfenadine	FLZ	Open-label, nonrandomized	Healthy volunteers	6	Inhibition of CYP3A4	Terfenadine AUC increased by ⩽100%	No clinical relevance, no action
[188]	Zidovudine	FLZ	Open-label, nonrandomized, parallel	HIV-infected patients	20	Inhibition of CYP2C9	Zidovudine AUC increased by ⩽100%	No clinical relevance
[189]	Zolpidem	ITZ	Open-label, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Zolpidem AUC increased by ⩽100%	No clinical relevance
[190]	Zopiclone	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	Zopiclone AUC and C_{max} increased by ⩽100%	No clinical relevance
Category A: no known interaction[e]								
[191]	Bromazepam	FLZ	Double-blind, randomized, crossover	Healthy volunteers	12	Unknown	No effect	No action
[192]	Clozapine	ITZ	Double-blind randomized	Psychiatric patients	7	Inhibition of CYP3A4	No effect	No clinical relevance, no action
[193]	Delavirdine	FLZ	Open-label, randomized, parallel	HIV-infected patients	13	Inhibition of CYP3A	No effect	No clinical relevance, no action
[194]	Didanosine	FLZ	Open-label, nonrandomized	HIV-infected patients	12	Unknown	No effect	No clinical relevance, no action
[166]	Didanosine (Videx EC)	FLZ	Open-label, randomized, crossover	Healthy volunteers	14	Unknown	No effect	No clinical relevance, no action
[195]	Digoxin	VRZ	Double-blind, randomized, placebo-controlled, parallel	Healthy volunteers	25	Unknown, possibly P-gP related	No effect	No clinical relevance, no action
[142]	Eprosartan	FLZ	Open-label, randomized, parallel	Healthy volunteers	16	Unknown	No effect	No action

[196]	Estazolam	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	No effect	No action
[63]	Fluvastatin	ITZ	Open-label, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	No effect	No action
[197]	Indinavir	FLZ	Double-blind, randomized, crossover	HIV-infected patients	13	Unknown	No effect	No action
[198]	Indinavir	VRZ	Study A: open-label, randomized, placebo-controlled; study B: double-blind, randomized, 2-way crossover	Healthy volunteers	Study A: 18; study B: 14	Inhibition of CYP3A4	Study A: no effect of indinavir on VRZ	No clinical relevance, no action
[199]	Lidocaine inhalation	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	No effect	No action
[200]	Mexiteline	FLZ	Open label, nonrandomized, crossover	Healthy volunteers	6	Unknown	No effect	No action
[201]	Omeprazole	FLZ	Randomized, crossover	Healthy volunteers	12	Stomach pH increase	No effect on FLZ	No action; see also category D for recommendation of omeprazole use
[202]	Pioglitazone	ITZ	Double-blind, randomized, crossover	Healthy volunteers	12	Inhibition of CYP3A4	No effect	No action
[105]	Pravastatine	FLZ	Double-blind, randomized, crossover	Healthy volunteers	12	Unknown	No effect	No action
[124]	Pravastatine	ITZ	Double-blind, randomized, crossover	Healthy volunteers	10	Inhibition of CYP3A4	No effect	No action

NOTE. All of the patients who participated in a study protocol were included in the number of participants. In the case of a controlled study, the control group was included in the total amount of participants. In the case of 2 research arms, both arms were included. "Antifungal agent" describes which antifungal agent is involved in the drug-drug interaction. More than 1 antifungal agent can be presented for a coadministered agent; this occurs when information on a drug interaction with an antifungal agent is presented with supposed different effects. In the case of multiple drugs being investigated, only the number of the patients who experienced in an azole interaction (including control group) is mentioned. The most plausible interaction mechanism is given. Some drug-drug interactions are based on theoretical considerations (e.g., because it is known that the drugs are metabolized by the same cytochrome protein [CYP] isoenzymes). Recommendations might reflect the opinions of the authors of the published articles but may also differ slightly, on the basis of interpretation from multiple studies and gathered information. Therapeutic drug monitoring (TDM) of selected azole antifungals is currently considered as an additional clinical tool, because relationships have been described between plasma concentrations and efficacy and/or toxicity [203–206]. A validated assay needs to be used to determine adequate plasma concentrations, and the interpretation of the results should be performed by a qualified person (e.g., clinical pharmacist and/or clinical pharmacologist). If a drug-drug interaction was not supported by a study, then it was based on another drug interaction with a coadministered agent that is structurally similar. In addition, the drug-drug interaction can be based on knowledge of the metabolic pathway of the drugs involved and/or the drugs' capacity to inhibit or induce this metabolic pathway. AUC, area under the concentration-time curve; BMT, bone marrow transplantation; CF, cystic fibrosis; CGD, chronic granulomatous disease; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CsA, cyclosporine A; C_{ss}, concentration in steady state; ESRD, end-stage renal disease; FLZ, fluconazole; hITZ, hydroxy-itraconazole; HIV, human immunodeficiency virus; HSCT, hematopoetic stem cell transplant; ICU, intensive care unit; ITZ, itraconazole; MAI, *Mycobacteria avium* infection; midazolam, MDZ; PD, Parkinson disease; P-gP, P-glycoprotein; PSZ, posaconazole; SCT, stem cell transplant; TAC, tacrolimus; VRZ, voriconazole.

[a] Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered to be contraindicated.

[b] Data demonstrate that the 2 medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empirical dosage adjustments, and/or choosing alternative agents.

[c] Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these 2 medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of 1 or both agents may be needed in a minority of patients.

[d] Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.

[e] Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.

Effect of Comedication on Azole Antifungal Drugs

Itraconazole and voriconazole are metabolized by the liver via phase I reactions. Voriconazole is a substrate for CYP2C19 and, to a lesser extent, for CYP2C9 and CYP3A4 [45, 46]. Itraconazole is predominantly metabolized by CYP3A4 and is the only azole antifungal drug with an active metabolite [13, 15]. Fluconazole is mainly excreted unchanged into the urine, and hepatic metabolism via CYP3A4 accounts for only 11% of the total drug excreted [6]. It is therefore unlikely that the interactions that influence the pharmacokinetic profile of fluconazole originated from this enzyme system. Posaconazole metabolism involves phase II reactions (i.e., glucuronidation of the drug) [32]. The drugs that influence phase II enzyme systems, such as lopinavir plus ritonavir [47], can exert a change in the pharmacokinetic profile of the azole drug involved, leading to increased or decreased exposure.

Genetic Polymorphism of CYP450 Enzyme Systems

All enzymes involved in the metabolism of azole antifungal drugs are known to have multiple polymorphisms that divide the population into poor metabolizers and extensive metabolizers. Patients who are homozygous or heterozygous poor metabolizers have a limited enzymatic capacity for the isoenzyme, which leads to a lower metabolic turnover of the drug involved and, thus, higher exposure. Polymorphisms of CYP2C9 and CYP2C19 may play a clinically relevant role, whereas polymorphisms of CYP3A4 are not considered clinically relevant. In homozygous poor metabolizers of CYP2C19, the C_{max} and AUC values of voriconazole are 2–5 times higher than those values in extensive metabolizers [48]. The CYP2C9 genotypic variation does not significantly influence the exposure to voriconazole, because only a small fraction of the drug is metabolized through this enzymatic pathway [49]. The prevalence of variations in the gene sequence differs by race, with 20%–30% of Asian persons and 2%–3% of white persons being homozygous poor metabolizers of CYP2C19 [50]. Determining the CYP2C19 genotype before initiation of therapy may predict possible toxicity; Asian patients might especially benefit from this approach. A cost-benefit analysis should be performed before using this approach in general practice. We do not recommend determining genotype before initiation of therapy, because the monitoring of plasma concentrations and clinical signs provide a better basis for management.

Drug Transporters

Active transporters, such as P-gP, organic anion-transporting polypeptides (OATPs), and breast cancer resistant protein (BCRP), play an important role in drug-drug interactions by regulating the access of drugs to the drug-metabolizing enzymes and by controlling drug concentrations in enterocytes and hepatocytes. Thus, the contribution of efflux transporters in drug-drug interactions cannot be excluded [16, 51]; however, there is a lack of convincing data on the clinical relevance of drug transporters.

P-gP. P-gP acts as an energy-dependent efflux pump that exports substrates out of the cell and is an important molecular determinant of oral bioavailability, brain penetration, and treatment resistance to several therapeutically used drugs. The modulation of the P-gP function may play a significant role in drug-drug interactions. Two azole antifungal drugs—itraconazole and posaconazole—are substrates for and inhibitors of P-gP of the multidrug resistance–1 gene [16, 28]. In vivo, no concrete relationship between azole antifungal drugs and P-gP has been established [51].

Other transporter systems. The OATP 1B1 is a multispecific carrier capable of bidirectional transportation across the sinusoidal liver membrane [52]. For instance, atorvastatin is subject to cellular membrane transport by OATP 1B1 and P-gP. It is suggested that itraconazole might block the transportation of atorvastatin because of the inhibition of the OATP 1B1 enzyme system [53]. The exact role of OATP, however, has not been established, and thus, its specific role in drug-drug interactions with selected substrates and inhibitors, such as itraconazole, remains unclear and requires further investigation.

The human BRCP belongs to the OATP-binding cassette transporter family. The BCRP does not seem to be inhibited by fluconazole or voriconazole. A simulation model has demonstrated that it is highly likely that the BCRP is inhibited by itraconazole [54]. In vivo, no relationship between azole antifungal drugs and the BCRP has been established.

RENAL EXCRETION

Drug interactions based on alterations in renal elimination mainly involve changes in tubular secretion or changes in kidney function. Drugs that use the same active transportation system in the kidney tubules can compete for this excretory system. The 2 drugs excreted by the kidneys are fluconazole and hydroxy-itraconazole. There have been no reports to date that have shown that impaired renal function caused by nephrotoxic drugs such as cyclosporine or gentamicin has led to increased toxicity of fluconazole or hydroxyl-itraconazole as a result of increased exposure.

PREDICTION OF DRUG-DRUG INTERACTIONS

Drug-drug interactions can cause many clinical problems. Ideally, comprehensive information should be available before a new drug completes the registration process. Because we aim for the maximum attainable therapeutic effect when treating invasive fungal disease, it is important to be aware of the mechanisms, whether theoretical or proven, behind drug-drug interactions. Currently, software tools are available that can fa-

cilitate rapid monitoring for interactions, thereby assisting in the clinical decision-making process.

Therapeutic drug monitoring. A drug-drug interaction is never straightforward, because not all patients will be effected to the same degree when they experience a drug-drug interaction. Therapeutic drug monitoring is an important tool for identifying the extent of the interaction and may help resolve actual and potential problems. Therapeutic drug monitoring can be used to guide dosing and to optimize therapy to prevent subtherapeutic effects or toxicity [55].

PRACTICAL ISSUES FOR USE OF THE DRUG-INTERACTION TABLE

Our drug-interaction table, which has a risk-ranking order of categories adapted from the UptoDate Lexi-Interact Tool [56] (table 1), provides an overview of drug-drug interactions published in peer-reviewed journals. The interactions that are most severe are listed first. This type of grading system helps the clinician to judge which drug combinations should be avoided and which drug combinations can be used safely. Futhermore, we have defined 9 areas of study that we consider to be necessary to review before making a judgement on the drug-drug interaction. In one area of study, various authors have provided recommendations on how to deal with the specific drug-drug interactions. Both the risk ranking and the recommendations reflect the opinions of the authors of the present article and are based on the interpretation of (multiple) studies and gathered information. Our recommendations may therefore differ slightly from the recommendations of the authors of the studies cited.

CONSIDERATIONS

We aimed to provide a comprehensive review of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents in the treatment of invasive fungal diseases. New information is emerging rapidly, and thus, this review is by its very nature incomplete. Awareness of the mechanisms involved in these interactions is pivotal for the optimization of treatment of patients requiring antifungal therapy. For the clinical interpretation, it should be kept in mind that much of the data presented in our review are from studies of healthy volunteers or a limited number of patients, and the clinical setting may therefore differ from the controlled setting of an interaction study. Drug-drug interactions do not only occur when therapy is initiated; they can also become evident after the drug therapy is stopped, particularly if the agent in question is an enzyme inducer, because this might lead to toxic concentrations.

Therapeutic drug monitoring is a valuable tool for assessing the effect of a drug-drug interaction for both the antifungal azole drug and, if possible, the coadministered drug. To perform therapeutic drug monitoring, a validated analytical method has to be available to determine whole blood or plasma concentrations. Assays have to be validated to ensure accuracy and precision. The measurement of samples can be done by in-house laboratory technicians, if facilities are available, or sent to reference laboratories with validated assays. The shorter the turnaround time (for instance, within 48 h), the better (for prompt patient management). Interpretation of the results can be performed by a clinical pharmacist and/or pharmacologist or by another health care professional who is familiar with therapeutic drug monitoring. Finally, addressing the problem of drug-drug interactions is a multidisciplinary task, with the goal of minimizing unwanted adverse effects while optimizing patient care.

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References

1. Eagling VA, Tjia JF, Back DJ. Differential selectivity of cytochrome P450 inhibitors against probe substrates in human and rat liver microsomes. Br J Clin Pharmacol **1998**; 45:107–14.
2. Guengerich FP. Comparisons of catalytic selectivity of cytochrome P450 subfamily enzymes from different species. Chem Biol Interact **1997**; 106:161–82.
3. US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Drugs@FDA: FDA approved drug products. DIFLUCAN. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=DIFLUCAN. Accessed 7 January 2008.
4. Pfaff G, Zimmermann T, Lach P, Yeates R, Simon G, Wildfeuer A. Pharmacokinetics and tolerance of fluconazole suppositories in healthy volunteers. Arzneimittelforschung **1993**; 43:391–5.
5. Buijk SL, Gyssens IC, Mouton JW, Verbrugh HA, Touw DJ, Bruining HA. Pharmacokinetics of sequential intravenous and enteral fluconazole in critically ill surgical patients with invasive mycoses and compromised gastro-intestinal function. Intensive Care Med **2001**; 27: 115–21.
6. 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**; 28:648–53.
7. Dudley MN. Clinical pharmacology of fluconazole. Pharmacotherapy **1990**; 10(6 Pt 3):S141–5.
8. Foulds G, Wajszczuk C, Weidler DJ, Garg DJ, Gibson P. Steady state parenteral kinetics of fluconazole in man. Ann N Y Acad Sci **1988**; 544:427–30.
9. de Beule K, Van Gestel J. Pharmacology of itraconazole. Drugs **2001**; 61(Suppl 1):27–37.
10. US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Drugs@FDA: FDA approved drug products. Search results for "sporanox." Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed 7 January 2008.
11. Barone JA, Moskovitz BL, Guarnieri J, et al. Enhanced bioavailability of itraconazole in hydroxypropyl-β-cyclodextrin solution versus capsules in healthy volunteers. Antimicrob Agents Chemother **1998**; 42: 1862–5.
12. Arredondo G, Martinez-Jorda R, Calvo R, Aguirre C, Suarez E. Protein binding of itraconazole and fluconazole in patients with chronic renal failure. Int J Clin Pharmacol Ther **1994**; 32:361–4.
13. Grant SM, Clissold SP. Itraconazole. A review of its pharmacodynamic

and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. Drugs **1989**; 37:310–44.
14. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. Ann Intern Med **1990**; 112: 108–12.
15. Bailey EM, Krakovsky DJ, Rybak MJ. The triazole antifungal agents: a review of itraconazole and fluconazole. Pharmacotherapy **1990**; 10: 146–53.
16. Wang EJ, Lew K, Casciano CN, Clement RP, Johnson WW. Interaction of common azole antifungals with P glycoprotein. Antimicrob Agents Chemother **2002**; 46:160–5.
17. 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**; 46:2546–53.
18. European Medicines Agency (EMEA). EPARs for authorised medicinal products for human use. Vfend. Available at: http://www.emea.europa.eu/htms/human/epar/v.htm. Accessed 7 January 2008.
19. Lutsar I, Roffey S, Troke P. Voriconazole concentrations in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. Clin Infect Dis **2003**; 37:728–32.
20. Verweij PE, Brinkman K, Kremer HP, Kullberg BJ, Meis JF. *Aspergillus* meningitis: diagnosis by non-culture-based microbiological methods and management. J Clin Microbiol **1999**; 37:1186–9.
21. Nulens E, Eggink C, Rijs AJ, Wesseling P, Verweij PE. Keratitis caused by *Scedosporium apiospermum* successfully treated with a cornea transplant and voriconazole. J Clin Microbiol **2003**; 41:2261–4.
22. Klont RR, Eggink CA, Rijs AJ, Wesseling P, Verweij PE. Successful treatment of *Fusarium* keratitis with cornea transplantation and topical and systemic voriconazole. Clin Infect Dis **2005**; 40:e110–2.
23. Hariprasad SM, Mieler WF, Holz ER, et al. Determination of vitreous, aqueous, and plasma concentration of orally administered voriconazole in humans. Arch Ophthalmol **2004**; 122:42–7.
24. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet **2006**; 45: 649–63.
25. Purkins L, Wood N, Greenhalgh K, Allen MJ, Oliver SD. Voriconazole, a novel wide-spectrum triazole: oral pharmacokinetics and safety. Br J Clin Pharmacol **2003**; 56(Suppl 1):10–6.
26. Purkins L, Wood N, Greenhalgh K, Eve MD, Oliver SD, Nichols D. The pharmacokinetics and safety of intravenous voriconazole—a novel wide-spectrum antifungal agent. Br J Clin Pharmacol **2003**; 56(Suppl 1):2–9.
27. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metab Dispos **2003**; 31:540–7.
28. European Medicines Agency (EMEA). EPARs for authorised medicinal products for human use. Noxafil. Available at: http://www.emea.europa.eu/htms/human/epar/n.htm. Accessed 7 January 2008.
29. 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**; 47:2788–95.
30. Keating GM. Posaconazole. Drugs **2005**; 65:1553–67.
31. Sansone-Parsons A, Krishna G, Simon J, et al. Effects of age, gender, and race/ethnicity on the pharmacokinetics of posaconazole in healthy volunteers. Antimicrob Agents Chemother **2007**; 51:495–502.
32. Ghosal A, Hapangama N, Yuan Y, et al. Identification of human UDP-glucuronosyltransferase enzyme(s) responsible for the glucuronidation of posaconazole (Noxafil). Drug Metab Dispos **2004**; 32:267–71.
33. 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: 3543–51.
34. Barone JA, Moskovitz BL, Guarnieri J, et al. Food interaction and steady-state pharmacokinetics of itraconazole oral solution in healthy volunteers. Pharmacotherapy **1998**; 18:295–301.
35. Purkins L, Wood N, Kleinermans D, Greenhalgh K, Nichols D. Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. Br J Clin Pharmacol **2003**; 56(Suppl 1):17–23.
36. Krishna G, Moton A, Ma L, et al. Effects of oral posaconazole on the pharmacokinetic properties of oral and intravenous midazolam: a phase I, randomized, open-label, crossover study in healthy volunteers. Clin Ther **2009**; 31:286–98.
37. 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**; 57:218–22.
38. Courtney R, Radwanski E, Lim J, Laughlin M. Pharmacokinetics of posaconazole coadministered with antacid in fasting or nonfasting healthy men. Antimicrob Agents Chemother **2004**; 48:804–8.
39. Sansone-Parsons A, Krishna G, Calzetta A, et al. Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers. Antimicrob Agents Chemother **2006**; 50:1881–3.
40. Blum RA, D'Andrea DT, Florentino BM, et al. Increased gastric pH and the bioavailability of fluconazole and ketoconazole. Ann Intern Med **1991**; 114:755–7.
41. Wood N, Tan K, Purkins L, et al. Effect of omeprazole on the steady-state pharmacokinetics of voriconazole. Br J Clin Pharmacol **2003**; 56(Suppl 1):56–61.
42. Gubbins PO, Krishna G, Sansone-Parsons A, et al. Pharmacokinetics and safety of oral posaconazole in neutropenic stem cell transplant recipients. Antimicrob Agents Chemother **2006**; 50:1993–9.
43. Black DJ, Kunze KL, Wienkers LC, et al. Warfarin-fluconazole. II. A metabolically based drug interaction: in vivo studies. Drug Metab Dispos **1996**; 24:422–8.
44. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. Clin Infect Dis **2003**; 36:630–7.
45. Purkins L, Wood N, Ghahramani P, Love ER, Eve MD, Fielding A. Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. Br J Clin Pharmacol **2003**; 56(Suppl 1):37–44.
46. Geist MJ, Egerer G, Burhenne J, Riedel KD, Mikus G. Induction of voriconazole metabolism by rifampin in a patient with acute myeloid leukemia: importance of interdisciplinary communication to prevent treatment errors with complex medications. Antimicrob Agents Chemother **2007**; 51:3455–6.
47. van der Lee MJ, Dawood L, ter Hofstede HJ, et al. Lopinavir/ritonavir reduces lamotrigine plasma concentrations in healthy subjects. Clin Pharmacol Ther **2006**; 80:159–68.
48. 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**; 75:587–8.
49. Geist MJ, Egerer G, Burhenne J, Mikus G. Safety of voriconazole in a patient with CYP2C9*2/CYP2C9*2 genotype. Antimicrob Agents Chemother **2006**; 50:3227–8.
50. Balian JD, Sukhova N, Harris JW, et al. The hydroxylation of omeprazole correlates with S-mephenytoin metabolism: a population study. Clin Pharmacol Ther **1995**; 57:662–9.
51. Venkatakrishnan K, Von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. Clin Pharmacokinet **2000**; 38:111–80.
52. Li L, Meier PJ, Ballatori N. Oatp2 mediates bidirectional organic solute transport: a role for intracellular glutathione. Mol Pharmacol **2000**; 58:335–40.
53. Lennernas H. Clinical pharmacokinetics of atorvastatin. Clin Pharmacokinet **2003**; 42:1141–60.
54. Gupta A, Unadkat JD, Mao Q. Interactions of azole antifungal agents with the human breast cancer resistance protein (BCRP). J Pharm Sci **2007**; 96:3226–35.
55. Brüggemann RJ, Donnelly JP, Aarnoutse RE, et al. Therapeutic drug monitoring of voriconazole. Ther Drug Monit **2008**; 30:403–11.
56. UptoDate. Lexi-Interact Online. Available at: http://www.uptodate.com/crlsql/interact/frameset.jsp. Accessed 16 December 2008.

57. Lohitnavy M, Lohitnavy O, Thangkeattiyanon O, Srichai W. Reduced oral itraconazole bioavailability by antacid suspension. J Clin Pharm Ther **2005**; 30:201–6.
58. Tucker RM, Denning DW, Hanson LH, et al. Interaction of azoles with rifampin, phenytoin, and carbamazepine: in vitro and clinical observations. Clin Infect Dis **1992**; 14:165–74.
59. May DB, Drew RH, Yedinak KC, Bartlett JA. Effect of simultaneous didanosine administration on itraconazole absorption in healthy volunteers. Pharmacotherapy **1994**; 14:509–13.
60. Naef R, Schmid C, Hofer M, Minder S, Speich R, Boehler A. Itraconazole comedication increases systemic levels of inhaled fluticasone in lung transplant recipients. Respiration **2007**; 74:418–22.
61. Penzak SR, Gubbins PO, Gurley BJ, Wang PL, Saccente M. Grapefruit juice decreases the systemic availability of itraconazole capsules in healthy volunteers. Ther Drug Monit **1999**; 21:304–9.
62. Neuvonen PJ, Jalava KM. Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. Clin Pharmacol Ther **1996**; 60:54–61.
63. Kivisto KT, Kantola T, Neuvonen PJ. Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. Br J Clin Pharmacol **1998**; 46:49–53.
64. Jaruratanasirikul S, Sriwiriyajan S. Effect of omeprazole on the pharmacokinetics of itraconazole. Eur J Clin Pharmacol **1998**; 54:159–61.
65. Ducharme MP, Slaughter RL, Warbasse LH, et al. Itraconazole and hydroxyitraconazole serum concentrations are reduced more than tenfold by phenytoin. Clin Pharmacol Ther **1995**; 58:617–24.
66. 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**; 23:1415–22.
67. Krishna G, Parsons A, Kantesaria B, Mant T. Evaluation of the pharmacokinetics of posaconazole and rifabutin following co-administration to healthy men. Curr Med Res Opin **2007**; 23:545–52.
68. Jaruratanasirikul S, Sriwiriyajan S. Effect of rifampicin on the pharmacokinetics of itraconazole in normal volunteers and AIDS patients. Eur J Clin Pharmacol **1998**; 54:155–8.
69. Marty FM, Lowry CM, Cutler CS, et al. Voriconazole and sirolimus coadministration after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **2006**; 12:552–9.
70. Rengelshausen J, Banfield M, Riedel KD, et al. Opposite effects of short-term and long-term St John's wort intake on voriconazole pharmacokinetics. Clin Pharmacol Ther **2005**; 78:25–33.
71. Honig PK, Wortham DC, Hull R, Zamani K, Smith JE, Cantilena LR. Itraconazole affects single-dose terfenadine pharmacokinetics and cardiac repolarization pharmacodynamics. J Clin Pharmacol **1993**; 33: 1201–6.
72. Neuvonen PJ, Varhe A, Olkkola KT. The effect of ingestion time interval on the interaction between itraconazole and triazolam. Clin Pharmacol Ther **1996**; 60:326–31.
73. Varhe A, Olkkola KT, Neuvonen PJ. Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther **1994**; 56(6 Pt 1):601–7.
74. Ariffin H, Omar KZ, Ang EL, Shekhar K. Severe vincristine neurotoxicity with concomitant use of itraconazole. J Paediatr Child Health **2003**; 39:638–9.
75. Bermudez M, Fuster JL, Llinares E, Galera A, Gonzalez C. Itraconazole-related increased vincristine neurotoxicity: case report and review of literature. J Pediatr Hematol Oncol **2005**; 27:389–92.
76. Bohme A, Ganser A, Hoelzer D. Aggravation of vincristine-induced neurotoxicity by itraconazole in the treatment of adult ALL. Ann Hematol **1995**; 71:311–2.
77. Gillies J, Hung KA, Fitzsimons E, Soutar R. Severe vincristine toxicity in combination with itraconazole. Clin Lab Haematol **1998**; 20:123–4.
78. Jeng MR, Feusner J. Itraconazole-enhanced vincristine neurotoxicity in a child with acute lymphoblastic leukemia. Pediatr Hematol Oncol **2001**; 18:137–42.
79. Kamaluddin M, McNally P, Breatnach F, et al. Potentiation of vincristine toxicity by itraconazole in children with lymphoid malignancies. Acta Paediatr **2001**; 90:1204–7.
80. Murphy JA, Ross LM, Gibson BE. Vincristine toxicity in five children with acute lymphoblastic leukaemia. Lancet **1995**; 346:443.
81. Sathiapalan RK, Al-Nasser A, El-Solh H, Al-Mohsen I, Al-Jumaah S. Vincristine-itraconazole interaction: cause for increasing concern. J Pediatr Hematol Oncol **2002**; 24:591.
82. Sathiapalan RK, El-Solh H. Enhanced vincristine neurotoxicity from drug interactions: case report and review of literature. Pediatr Hematol Oncol **2001**; 18:543–6.
83. Palkama VJ, Isohanni MH, Neuvonen PJ, Olkkola KT. The effect of intravenous and oral fluconazole on the pharmacokinetics and pharmacodynamics of intravenous alfentanil. Anesth Analg **1998**; 87: 190–4.
84. Saari TI, Laine K, Leino K, Valtonen M, Neuvonen PJ, Olkkola KT. Voriconazole, but not terbinafine, markedly reduces alfentanil clearance and prolongs its half-life. Clin Pharmacol Ther **2006**; 80:502–8.
85. Newberry DL, Bass SN, Mbanefo CO. A fluconazole/amitriptyline drug interaction in three male adults. Clin Infect Dis **1997**; 24:270–1.
86. Kantola T, Kivisto KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atorvastatin. Clin Pharmacol Ther **1998**; 64: 58–65.
87. Raaska K, Niemi M, Neuvonen M, Neuvonen PJ, Kivisto KT. Plasma concentrations of inhaled budesonide and its effects on plasma cortisol are increased by the cytochrome P4503A4 inhibitor itraconazole. Clin Pharmacol Ther **2002**; 72:362–9.
88. Skov M, Main KM, Sillesen IB, Muller J, Koch C, Lanng S. Iatrogenic adrenal insufficiency as a side-effect of combined treatment of itraconazole and budesonide. Eur Respir J **2002**; 20:127–33.
89. Christensen J, Dupont E, Ostergaard K. Cabergoline plasma concentration is increased during concomitant treatment with itraconazole. Mov Disord **2002**; 17:1360–2.
90. Lilja JJ, Backman JT, Laitila J, Luurila H, Neuvonen PJ. Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. Clin Pharmacol Ther **2003**; 73:192–8.
91. Canafax DM, Graves NM, Hilligoss DM, Carleton BC, Gardner MJ, Matas AJ. Interaction between cyclosporine and fluconazole in renal allograft recipients. Transplantation **1991**; 51:1014–8.
92. Sud K, Singh B, Krishna VS, et al. Unpredictable cyclosporin–fluconazole interaction in renal transplant recipients. Nephrol Dial Transplant **1999**; 14:1698–703.
93. Osowski CL, Dix SP, Lin LS, Mullins RE, Geller RB, Wingard JR. Evaluation of the drug interaction between intravenous high-dose fluconazole and cyclosporine or tacrolimus in bone marrow transplant patients. Transplantation **1996**; 61:1268–72.
94. Florea NR, Capitano B, Nightingale CH, Hull D, Leitz GJ, Nicolau DP. Beneficial pharmacokinetic interaction between cyclosporine and itraconazole in renal transplant recipients. Transplant Proc **2003**; 35: 2873–7.
95. 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**; 12:325–34.
96. 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**; 27:825–34.
97. Romero AJ, Le PP, Nilsson LG, Wood N. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. Clin Pharmacol Ther **2002**; 71:226–34.
98. Karyekar CS, Eddington ND, Briglia A, Gubbins PO, Dowling TC. Renal interaction between itraconazole and cimetidine. J Clin Pharmacol **2004**; 44:919–27.
99. Hynninen VV, Olkkola KT, Leino K, et al. Effect of voriconazole on the pharmacokinetics of diclofenac. Fundam Clin Pharmacol **2007**; 21:651–6.

100. Jalava KM, Partanen J, Neuvonen PJ. Itraconazole decreases renal clearance of digoxin. Ther Drug Monit **1997**; 19:609–13.
101. Liu P, Foster G, Labadie RR, Gutierrez MJ, Sharma A. Pharmacokinetic interaction between voriconazole and efavirenz at steady state in healthy male subjects. J Clin Pharmacol **2008**; 48:73–84.
102. Damle B, Labadie R, Crownover P, Glue P. Pharmacokinetic interactions of efavirenz and voriconazole in healthy volunteers. Br J Clin Pharmacol **2008**; 65:523–30.
103. Andrews E, Damle BD, Fang A, et al. Pharmacokinetics and tolerability of voriconazole and a combination oral contraceptive co-administered in healthy female subjects. Br J Clin Pharmacol **2008**; 65: 531–9.
104. Jalava KM, Olkkola KT, Neuvonen PJ. Itraconazole greatly increases plasma concentrations and effects of felodipine. Clin Pharmacol Ther **1997**; 61:410–5.
105. Kantola T, Backman JT, Niemi M, Kivisto KT, Neuvonen PJ. Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. Eur J Clin Pharmacol **2000**; 56:225–9.
106. Niemi M, Backman JT, Neuvonen M, Laitila J, Neuvonen PJ, Kivisto KT. Effects of fluconazole and fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. Clin Pharmacol Ther **2001**; 69:194–200.
107. Liu P, Foster G, Labadie R, Somoza E, Sharma A. Pharmacokinetic interaction between voriconazole and methadone at steady state in patients on methadone therapy. Antimicrob Agents Chemother **2007**; 51: 110–8.
108. Ahonen J, Olkkola KT, Neuvonen PJ. Effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. Eur J Clin Pharmacol **1997**; 51:415–9.
109. Ahonen J, Olkkola KT, Takala A, Neuvonen PJ. Interaction between fluconazole and midazolam in intensive care patients. Acta Anaesthesiol Scand **1999**; 43:509–14.
110. Olkkola KT, Ahonen J, Neuvonen PJ. The effects of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. Anesth Analg **1996**; 82:511–6.
111. Vanakoski J, Mattila MJ, Vainio P, Idanpaan-Heikkila JJ, Tornwall M. 150 mg fluconazole does not substantially increase the effects of 10 mg midazolam or the plasma midazolam concentrations in healthy subjects. Int J Clin Pharmacol Ther **1995**; 33:518–23.
112. Ahonen J, Olkkola KT, Neuvonen PJ. Effect of itraconazole and terbinafine on the pharmacokinetics and pharmacodynamics of midazolam in healthy volunteers. Br J Clin Pharmacol **1995**; 40:270–2.
113. Backman JT, Kivisto KT, Olkkola KT, Neuvonen PJ. The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. Eur J Clin Pharmacol **1998**; 54:53–8.
114. Olkkola KT, Backman JT, Neuvonen PJ. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther **1994**; 55:481–5.
115. 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**; 21:645–53.
116. 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**; 79:362–70.
117. Garazzino S, Tettoni M, Calcagno A, D'Avolio A, Bonora S, Di Perri G. Ritonavir-dependent fluconazole boosting of nelfinavir: a report of three cases. J Antimicrob Chemother **2006**; 58:483–5.
118. Jaruratanasirikul S, Sriwiriyajan S. Pharmacokinetic study of the interaction between itraconazole and nevirapine. Eur J Clin Pharmacol **2007**; 63:451–6.
119. Kang BC, Yang CQ, Cho HK, Suh OK, Shin WG. Influence of fluconazole on the pharmacokinetics of omeprazole in healthy volunteers. Biopharm Drug Dispos **2002**; 23:77–81.
120. Blum RA, Wilton JH, Hilligoss DM, et al. Effect of fluconazole on the disposition of phenytoin. Clin Pharmacol Ther **1991**; 49:420–5.
121. Liu P, Foster G, Gandelman K, et al. Steady-state pharmacokinetic and safety profiles of voriconazole and ritonavir in healthy male subjects. Antimicrob Agents Chemother **2007**; 51:3617–26.
122. Mikus G, Schowel V, Drzewinska M, et al. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. Clin Pharmacol Ther **2006**; 80:126–35.
123. Cardiello PG, Samor T, Burger D, et al. Pharmacokinetics of lower doses of saquinavir soft-gel caps (800 and 1200 mg twice daily) boosted with itraconazole in HIV-1-positive patients. Antivir Ther **2003**; 8:245–9.
124. Neuvonen PJ, Kantola T, Kivisto KT. Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. Clin Pharmacol Ther **1998**;63:332–41.
125. Manez R, Martin M, Raman D, et al. Fluconazole therapy in transplant recipients receiving FK506. Transplantation **1994**; 57:1521–3.
126. Shitrit D, Ollech JE, Ollech A, et al. Itraconazole prophylaxis in lung transplant recipients receiving tacrolimus (FK 506): efficacy and drug interaction. J Heart Lung Transplant **2005**; 24:2148–52.
127. Saari TI, Laine K, Leino K, Valtonen M, Neuvonen PJ, Olkkola KT. Effect of voriconazole on the pharmacokinetics and pharmacodynamics of zolpidem in healthy subjects. Br J Clin Pharmacol **2007**; 63:116–20.
128. Yasui N, Kondo T, Otani K, et al. Effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of alprazolam. Psychopharmacology (Berl) **1998**; 139:269–73.
129. Furukori H, Kondo T, Yasui N, et al. Effects of itraconazole on the steady-state plasma concentrations of bromperidol and reduced bromperidol in schizophrenic patients. Psychopharmacology (Berl) **1999**; 145: 189–92.
130. Purkins L, Wood N, Kleinermans D, Nichols D. Histamine H2-receptor antagonists have no clinically significant effect on the steady-state pharmacokinetics of voriconazole. Br J Clin Pharmacol **2003**; 56(Suppl 1):51–5.
131. Auclair B, Berning SE, Huitt GA, Peloquin CA. Potential interaction between itraconazole and clarithromycin. Pharmacotherapy **1999**; 19: 1439–44.
132. Marr KA, Leisenring W, Crippa F, et al. Cyclophosphamide metabolism is affected by azole antifungals. Blood **2004**; 103:1557–9.
133. 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**; 68:487–94.
134. Saari TI, Laine K, Bertilsson L, Neuvonen PJ, Olkkola KT. Voriconazole and fluconazole increase the exposure to oral diazepam. Eur J Clin Pharmacol **2007**; 63:941–9.
135. Ahonen J, Olkkola KT, Neuvonen PJ. The effect of the antimycotic itraconazole on the pharmacokinetics and pharmacodynamics of diazepam. Fundam Clin Pharmacol **1996**; 10:314–8.
136. Araki K, Yasui-Furukori N, Fukasawa T, et al. Inhibition of the metabolism of etizolam by itraconazole in humans: evidence for the involvement of CYP3A4 in etizolam metabolism. Eur J Clin Pharmacol **2004**; 60:427–30.
137. Saari TI, Laine K, Neuvonen M, Neuvonen PJ, Olkkola KT. Effect of voriconazole and fluconazole on the pharmacokinetics of intravenous fentanyl. Eur J Clin Pharmacol **2008**; 64:25–30.
138. Palkama VJ, Neuvonen PJ, Olkkola KT. The CYP 3A4 inhibitor itraconazole has no effect on the pharmacokinetics of i.v. fentanyl. Br J Anaesth **1998**; 81:598–600.
139. Park JY, Shon JH, Kim KA, et al. Combined effects of itraconazole and CYP2D6*10 genetic polymorphism on the pharmacokinetics and pharmacodynamics of haloperidol in healthy subjects. J Clin Psychopharmacol **2006**; 26:135–42.
140. Hynninen VV, Olkkola KT, Leino K, et al. Effects of the antifungals

voriconazole and fluconazole on the pharmacokinetics of s-(+)- and R-(−)-Ibuprofen. Antimicrob Agents Chemother **2006**; 50:1967–72.
141. Niemi M, Tornio A, Pasanen MK, Fredrikson H, Neuvonen PJ, Backman JT. Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. Eur J Clin Pharmacol **2006**; 62:463–72.
142. Kazierad DJ, Martin DE, Blum RA, et al. Effect of fluconazole on the pharmacokinetics of eprosartan and losartan in healthy male volunteers. Clin Pharmacol Ther **1997**; 62:417–25.
143. Kaukonen KM, Olkkola KT, Neuvonen PJ. Fluconazole but not itraconazole decreases the metabolism of losartan to E-3174. Eur J Clin Pharmacol **1998**; 53:445–9.
144. Varis T, Kivisto KT, Backman JT, Neuvonen PJ. Itraconazole decreases the clearance and enhances the effects of intravenously administered methylprednisolone in healthy volunteers. Pharmacol Toxicol **1999**; 85:29–32.
145. Masui T, Kusumi I, Takahashi Y, Koyama T. Effects of itraconazole and tandospirone on the pharmacokinetics of perospirone. Ther Drug Monit **2006**; 28:73–5.
146. Damkier P, Hansen LL, Brosen K. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. Br J Clin Pharmacol **1999**; 48:829–38.
147. Kaukonen KM, Olkkola KT, Neuvonen PJ. Itraconazole increases plasma concentrations of quinidine. Clin Pharmacol Ther **1997**; 62: 510–7.
148. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. Diabetologia **2003**; 46: 347–51.
149. Trapnell CB, Narang PK, Li R, Lavelle JP. Increased plasma rifabutin levels with concomitant fluconazole therapy in HIV-infected patients. Ann Intern Med **1996**; 124:573–6.
150. Jordan MK, Polis MA, Kelly G, Narang PK, Masur H, Piscitelli SC. Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. Antimicrob Agents Chemother **2000**; 44:2170–2.
151. Jaruratanasirikul S, Kleepkaew A. Lack of effect of fluconazole on the pharmacokinetics of rifampicin in AIDS patients. J Antimicrob Chemother **1996**; 38:877–80.
152. Panomvana Na Ayudhya D, Thanompuangseree N, Tansuphaswadikul S. Effect of rifampicin on the pharmacokinetics of fluconazole in patients with AIDS. Clin Pharmacokinet **2004**; 43:725–32.
153. Nicolau DP, Crowe HM, Nightingale CH, Quintiliani R. Rifampin-fluconazole interaction in critically ill patients. Ann Pharmacother **1995**; 29:994–6.
154. Jung SM, Kim KA, Cho HK, et al. Cytochrome P450 3A inhibitor itraconazole affects plasma concentrations of risperidone and 9-hydroxyrisperidone in schizophrenic patients. Clin Pharmacol Ther **2005**; 78:520–8.
155. Jokinen MJ, Ahonen J, Neuvonen PJ, Olkkola KT. Effect of clarithromycin and itraconazole on the pharmacokinetics of ropivacaine. Pharmacol Toxicol **2001**; 88:187–91.
156. Varhe A, Olkkola KT, Neuvonen PJ. Fluconazole, but not terbinafine, enhances the effects of triazolam by inhibiting its metabolism. Br J Clin Pharmacol **1996**; 41:319–23.
157. Varhe A, Olkkola KT, Neuvonen PJ. Effect of fluconazole dose on the extent of fluconazole-triazolam interaction. Br J Clin Pharmacol **1996**; 42:465–70.
158. Hynninen VV, Olkkola KT, Bertilsson L, Kurkinen K, Neuvonen PJ, Laine K. Effect of terbinafine and voriconazole on the pharmacokinetics of the antidepressant venlafaxine. Clin Pharmacol Ther **2008**; 83:342–8.
159. Purkins L, Wood N, Kleinermans D, Nichols D. Voriconazole potentiates warfarin-induced prothrombin time prolongation. Br J Clin Pharmacol **2003**; 56(Suppl 1):24–9.
160. Kubo M, Koue T, Inaba A, et al. Influence of itraconazole co-administration and CYP2D6 genotype on the pharmacokinetics of the new antipsychotic ARIPIPRAZOLE. Drug Metab Pharmacokinet **2005**; 20: 55–64.
161. Lilja JJ, Backman JT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atenolol. Basic Clin Pharmacol Toxicol **2005**; 97: 395–8.
162. Purkins L, Wood N, Ghahramani P, Kleinermans D, Layton G, Nichols D. No clinically significant effect of erythromycin or azithromycin on the pharmacokinetics of voriconazole in healthy male volunteers. Br J Clin Pharmacol **2003**; 56(Suppl 1):30–6.
163. Palkama VJ, Neuvonen PJ, Olkkola KT. Effect of itraconazole on the pharmacokinetics of bupivacaine enantiomers in healthy volunteers. Br J Anaesth **1999**; 83:659–61.
164. Buggia I, Zecca M, Alessandrino EP, 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**; 16:2083–8.
165. Winter HR, Trapnell CB, Slattery JT, et al. The effect of clarithromycin, fluconazole, and rifabutin on sulfamethoxazole hydroxylamine formation in individuals with human immunodeficiency virus infection (AACTG 283). Clin Pharmacol Ther **2004**; 76:313–22.
166. Damle B, Hess H, Kaul S, Knupp C. Absence of clinically relevant drug interactions following simultaneous administration of didanosine-encapsulated, enteric-coated bead formulation with either itraconazole or fluconazole. Biopharm Drug Dispos **2002**; 23:59–66.
167. Sinofsky FE, Pasquale SA. The effect of fluconazole on circulating ethinyl estradiol levels in women taking oral contraceptives. Am J Obstet Gynecol **1998**; 178:300–4.
168. Hilbert J, Messig M, Kuye O, Friedman H. Evaluation of interaction between fluconazole and an oral contraceptive in healthy women. Obstet Gynecol **2001**; 98:218–23.
169. Kovarik JM, Hsu CH, McMahon L, Berthier S, Rordorf C. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedications. Clin Pharmacol Ther **2001**; 70:247–54.
170. Shimizu M, Uno T, Sugawara K, Tateishi T. Effects of single and multiple doses of itraconazole on the pharmacokinetics of fexofenadine, a substrate of P-glycoprotein. Br J Clin Pharmacol **2006**; 62: 372–6.
171. Shon JH, Yoon YR, Hong WS, et al. Effect of itraconazole on the pharmacokinetics and pharmacodynamics of fexofenadine in relation to the MDR1 genetic polymorphism. Clin Pharmacol Ther **2005**; 78: 191–201.
172. Uno T, Shimizu M, Sugawara K, Tateishi T. Lack of dose-dependent effects of itraconazole on the pharmacokinetic interaction with fexofenadine. Drug Metab Dispos **2006**; 34:1875–9.
173. Swaisland HC, Ranson M, Smith RP, et al. Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. Clin Pharmacokinet **2005**; 44:1067–81.
174. Gubbins PO, McConnell SA, Gurley BJ, et al. Influence of grapefruit juice on the systemic availability of itraconazole oral solution in healthy adult volunteers. Pharmacotherapy **2004**; 24:460–7.
175. Ouellet D, Bramson C, Roman D, et al. Effects of three cytochrome P450 inhibitors, ketoconazole, fluconazole, and paroxetine, on the pharmacokinetics of lasofoxifene. Br J Clin Pharmacol **2007**; 63:59–66.
176. Isohanni MH, Neuvonen PJ, Palkama VJ, Olkkola KT. Effect of erythromycin and itraconazole on the pharmacokinetics of intravenous lignocaine. Eur J Clin Pharmacol **1998**; 54:561–5.
177. Isohanni MH, Neuvonen PJ, Olkkola KT. Effect of erythromycin and itraconazole on the pharmacokinetics of oral lignocaine. Pharmacol Toxicol **1999**; 84:143–6.
178. Scott G, Yih L, Yeh CM, Milosavljev S, Laurent A, Rordorf C. Lumiracoxib: pharmacokinetic and pharmacodynamic profile when coadministered with fluconazole in healthy subjects. J Clin Pharmacol **2004**; 44:193–9.

179. Johnson MD, Hamilton CD, Drew RH, Sanders LL, Pennick GJ, Perfect JR. A randomized comparative study to determine the effect of omeprazole on the peak serum concentration of itraconazole oral solution. J Antimicrob Chemother **2003**; 51:453–7.
180. Lukkari E, Juhakoski A, Aranko K, Neuvonen PJ. Itraconazole moderately increases serum concentrations of oxybutynin but does not affect those of the active metabolite. Eur J Clin Pharmacol **1997**; 52: 403–6.
181. Varis T, Kivisto KT, Neuvonen PJ. The effect of itraconazole on the pharmacokinetics and pharmacodynamics of oral prednisolone. Eur J Clin Pharmacol **2000**; 56:57–60.
182. Cato A III, Cao G, Hsu A, Cavanaugh J, Leonard J, Granneman R. Evaluation of the effect of fluconazole on the pharmacokinetics of ritonavir. Drug Metab Dispos **1997**; 25:1104–6.
183. Koks CH, Crommentuyn KM, Hoetelmans RM, et al. The effect of fluconazole on ritonavir and saquinavir pharmacokinetics in HIV-1-infected individuals. Br J Clin Pharmacol **2001**; 51:631–5.
184. Cooper KJ, Martin PD, Dane AL, Warwick MJ, Schneck DW, Cantarini MV. The effect of fluconazole on the pharmacokinetics of rosuvastatin. Eur J Clin Pharmacol **2002**; 58:527–31.
185. Cooper KJ, Martin PD, Dane AL, Warwick MJ, Schneck DW, Cantarini MV. Effect of itraconazole on the pharmacokinetics of rosuvastatin. Clin Pharmacol Ther **2003**; 73:322–9.
186. Ahonen J, Olkkola KT, Neuvonen PJ. Lack of effect of antimycotic itraconazole on the pharmacokinetics or pharmacodynamics of temazepam. Ther Drug Monit **1996**; 18:124–7.
187. Honig PK, Worham DC, Zamani K, Mullin JC, Conner DP, Cantilena LR. The effect of fluconazole on the steady-state pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine in humans. Clin Pharmacol Ther **1993**; 53:630–6.
188. Brockmeyer NH, Tillmann I, Mertins L, Barthel B, Goos M. Pharmacokinetic interaction of fluconazole and zidovudine in HIV-positive patients. Eur J Med Res **1997**; 2:377–83.
189. Luurila H, Kivisto KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics and pharmacodynamics of zolpidem. Eur J Clin Pharmacol **1998**; 54:163–6.
190. Jalava KM, Olkkola KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics and pharmacodynamics of zopiclone. Eur J Clin Pharmacol **1996**; 51:331–4.
191. Ohtani Y, Kotegawa T, Tsutsumi K, Morimoto T, Hirose Y, Nakano S. Effect of fluconazole on the pharmacokinetics and pharmacodynamics of oral and rectal bromazepam: an application of electroencephalography as the pharmacodynamic method. J Clin Pharmacol **2002**; 42:183–91.
192. Raaska K, Neuvonen PJ. Serum concentrations of clozapine and N-desmethylclozapine are unaffected by the potent CYP3A4 inhibitor itraconazole. Eur J Clin Pharmacol **1998**; 54:167–70.
193. Borin MT, Cox SR, Herman BD, Carel BJ, Anderson RD, Freimuth WW. Effect of fluconazole on the steady-state pharmacokinetics of delavirdine in human immunodeficiency virus-positive patients. Antimicrob Agents Chemother **1997**; 41:1892–7.
194. Bruzzese VL, Gillum JG, Israel DS, Johnson GL, Kaplowitz LG, Polk RE. Effect of fluconazole on pharmacokinetics of 2',3'-dideoxyinosine in persons seropositive for human immunodeficiency virus. Antimicrob Agents Chemother **1995**; 39:1050–3.
195. Purkins L, Wood N, Kleinermans D, Nichols D. Voriconazole does not affect the steady-state pharmacokinetics of digoxin. Br J Clin Pharmacol **2003**; 56(Suppl 1):45–50.
196. Otsuji Y, Okuyama N, Aoshima T, et al. No effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of estazolam. Ther Drug Monit **2002**; 24:375–8.
197. De Wit S, Debier M, De Smet M, et al. Effect of fluconazole on indinavir pharmacokinetics in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother **1998**; 42:223–7.
198. Purkins L, Wood N, Kleinermans D, Love ER. No clinically significant pharmacokinetic interactions between voriconazole and indinavir in healthy volunteers. Br J Clin Pharmacol **2003**; 56(Suppl 1):62–8.
199. Isohanni MH, Neuvonen PJ, Olkkola KT. Effect of itraconazole on the pharmacokinetics of inhaled lidocaine. Basic Clin Pharmacol Toxicol **2004**; 95:120–3.
200. Ueno K, Yamaguchi R, Tanaka K, et al. Lack of a kinetic interaction between fluconazole and mexiletine. Eur J Clin Pharmacol **1996**; 50: 129–31.
201. Zimmermann T, Yeates RA, Riedel KD, Lach P, Laufen H. The influence of gastric pH on the pharmacokinetics of fluconazole: the effect of omeprazole. Int J Clin Pharmacol Ther **1994**; 32:491–6.
202. Jaakkola T, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics of pioglitazone. Clin Pharmacol Ther **2005**; 77:404–14.
203. Buchkowsky SS, Partovi N, Ensom MH. Clinical pharmacokinetic monitoring of itraconazole is warranted in only a subset of patients. Ther Drug Monit **2005**; 27:322–33.
204. Dominguez-Gil HA, Sanchez NA, Garcia Sanchez MJ. Therapeutic drug monitoring of itraconazole and the relevance of pharmacokinetic interactions. Clin Microbiol Infect **2006**; 12(Suppl 7):97–106.
205. Smith J, Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother **2006**; 50:1570–2.
206. Trifilio S, Ortiz R, Pennick G, et al. Voriconazole therapeutic drug monitoring in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant **2005**; 35:509–13.