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Systemic Antifungal Agents
Drug Interactions of Clinical Significance

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Summary

There are 3 main classes of systemic antifungals: the polyene macrolides (e.g. amphotericin B), the azoles (e.g. the imidazoles ketoconazole and miconazole and the triazoles itraconazole and fluconazole) and the allylamines (e.g. terbinafine). Other systemic antifungals include griseofulvin and flucytosine.

Most drug-drug interactions involving systemic antifungals have negative consequences. The interactions of amphotericin B, flucytosine, griseofulvin, terbinafine and azole antifungals can be divided into the following categories: (i) additive dangerous interactions; (ii) modifications of antifungal kinetics by other drugs; and (iii) modifications of the kinetics of other drugs by antifungals.

Amphotericin B and flucytosine mainly interact with other agents pharmacodynamically. Clinically important drug interactions with amphotericin B cause nephrotoxicity, hypokalaemia and blood dyscrasias. The most important drug interaction of flucytosine occurs with myelotoxic agents.

Hypokalaemia can precipitate the long QT syndrome, as well as potentially lethal ventricular arrhythmias like torsade de pointes. Synergism is likely to occur when either QT interval–modifying drugs (e.g. terfenadine and astemizole) and drugs that induce hypokalaemia (e.g. amphotericin B) are coadministered.

Induction and inhibition of cytochrome P450 enzymes at hepatic and extrahepatic sites are the mechanisms that underlie the most serious pharmacokinetic drug interactions of the azole antifungals. These agents have been shown to notably decrease the catabolism of numerous drugs: histamine H_1 receptor antago-

nists, warfarin, cyclosporin, tacrolimus, digoxin, felodipine, lovastatin, midazolam, triazolam, methylprednisolone, glibenclamide (glyburide), phenytoin, rifabutin, ritonavir, saquinavir, nevirapine and nortriptyline. Non-antifungal drugs like carbamazepine, phenobarbital (phenobarbitone), phenytoin and rifampicin (rifampin) can induce the metabolism of azole antifungals. The bioavailability of ketoconazole and itraconazole is also reduced by drugs that increase gastric pH, such as H_2 receptor antagonists, proton pump inhibitors, sucralfate and didanosine.

Griseofulvin is an enzymatic inducer of coumarin-like drugs and estrogens, whereas terbinafine seems to have a low potential for drug interactions.

Despite important advances in our understanding of the mechanisms underlying pharmacokinetic drug interactions during the 1990s, at this time they still remain difficult to predict in terms of magnitude in individual patients. This is because of the large interindividual and intraindividual variations in the catalytic activity of those metabolising enzymes that can either be induced or inhibited by various drugs. Notwithstanding these variations, increasing clinical experience is allowing pharmacokinetic interactions to be used to advantage in order to improve the tolerability of some drugs, as recently exemplified by the use of a fixed combination of ketoconazole and cyclosporin.

Systemic antifungals act through a variety of mechanisms, and interactions with a large number of coprescribed drugs have been described. These can be classified into 2 categories: those involving modifications in the rate of metabolism (pharmacokinetic interactions) and those that result from additive or inhibitory effects at a common site or different sites in an organ (pharmacodynamic interactions). *In vivo* studies, case reports, clinical observations and general reviews have been published on systemic antifungal drug interactions. Most of these interactions have been substantiated, but some are only suspected from proposed mechanisms and reports in the literature are rare or conflicting. The purpose of this review is to define and clarify the most clinically relevant and recently reported drug interactions of systemic antifungals; that is, interactions which may result in unwanted effects, increased toxicity or loss of efficacy.

1. Pharmacodynamic Interactions

Pharmacodynamic interactions result from the effect of drugs on the same physiological processes, and they often, but not always, involve occupation of receptor sites. They are generally easy to predict from the respective pharmacological properties of coadministered drugs. Despite the fact that they are not pharmacokinetic in nature, the clearance of drugs can be modified when the functional integrity of organs through which they are cleared from the body is severely impaired by additive toxicity.

1.1 Amphotericin B

The pharmacodynamic interactions of amphotericin B are listed in table I.

Amphotericin B is a polyene antifungal that is reserved for the treatment of serious infections because of its low therapeutic index. It is not orally or intramuscularly absorbed. It is extensively distributed to, and slowly released from, tissues (its second elimination half-life is about 15 days). Although only 5% of the drug is excreted unchanged by the kidney, no metabolites have been identified, and the drug is thought to be released from a central compartment (volume of distribution 4 L/kg).

Clinically important clinical drug interactions of amphotericin B may be divided into 3 categories: (i) nephrotoxic interactions, which result from direct and additive deleterious effects on renal

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Table I. Clinically significant pharmacodynamic drug interactions with amphotericin B. In general, these interactions are caused by additive pharmacological effects that are directed to only 1 target organ or function and are dose-dependent

Interacting drug	Adverse effect	Mechanism
Antineoplastic agents (nitrosoureas)[a]	Nephrotoxicity	Direct tubular and glomerular toxicity
Aminoglycosides[a]	Nephrotoxicity	Direct tubular and glomerular toxicity
Cyclosporin[a]	Nephrotoxicity	Direct tubular toxicity, arteriolopathy sparing glomerular arterioles, interstitial fibrosis
Tacrolimus[a]	Nephrotoxicity	Direct tubular toxicity, arteriolopathy sparing glomerular arterioles, interstitial fibrosis
Pentamidine[a]	Nephrotoxicity	Decreased renal function due to potent inhibition of kidney dihydrofolate reductase
Foscarnet[a]	Nephrotoxicity	Direct tubular toxicity
Tubocurarine	Increased muscle relaxant effect	Muscle relaxant effect increased by amphotericin B–induced hypokalaemia
Zidovudine (and other drugs known to be myelotoxic at therapeutic concentrations)[b]	Haematological toxicity (e.g. hypochromic monocytic anaemia, thrombocytopenia, leucopenia)	
Hypokalaemic drugs		
Corticotrophin[c]	Hypokalaemia	
Non–potassium sparing diuretics[c]	Hypokalaemia	
Hydrocortisone[c]	Hypokalaemia	
Stimulant laxatives[c]	Hypokalaemia	
Drugs whose cardiotoxicity can be enhanced by potassium loss		
Digitalis	Hypokalaemia	Decrease in potassium levels in serum and tissues increases automaticity and promotes inhibition of Na^+,K^+ATPase by digitalis
Cardioactive drugs that induce torsade de pointes		
Amiodarone[d]	Torsade de pointes	
Bepridil[d]	Torsade de pointes	
Disopyramide[d]	Torsade de pointes	
Quinidine[d,e]	Torsade de pointes	
Sotalol[d]	Torsade de pointes	
Noncardioactive drugs that induce torsade de pointes		
Astemizole[d]	Torsade de pointes	
Erythromycin[d]	Torsade de pointes	
Halofantrine[d]	Torsade de pointes	
Pentamidine[d]	Torsade de pointes	
Terfenadine[d]	Torsade de pointes	
Sultopride[d]	Torsade de pointes	
Vincamine[d]	Torsade de pointes	

a Interactions moderate to major in severity; the combination of amphotericin B and these drugs is best avoided. If this is not possible, intensive monitoring of renal function is recommended and caution should be used regarding posology of drugs that are eliminated unchanged by the renal route.

b Interactions major to life-threatening in severity; combination of amphotericin B and these drugs are best avoided. It is advisable to monitor blood counts on a regular basis.

c Interactions are moderate in severity; combination of amphotericin B and these drugs is best avoided. If this is not possible, potassium level monitoring is indicated.

d Hypokalaemia is induced by amphotericin B and increases the risk of drug-induced torsade de pointes; interactions moderate to major in severity. Combination of amphotericin B and these drugs is best avoided; serum potassium levels should be monitored and deficiencies corrected.

e Interactions major to life-threatening in severity with quinidine because quinidine-induced torsade de pointes can occur at therapeutic or even subtherapeutic concentrations.

Abbreviation: ATP = adenosine triphosphate.

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structures, principally the tubules; (ii) drug interactions for which hypokalaemia represents a common underlying factor that facilitates drug toxicity directed to cardiac and skeletal muscles; and (iii) blood dyscrasias which result from myelotoxic interactions.[1-10]

Amphotericin B is used extensively for the treatment of deep-seated fungal infections. Therefore, it is commonly part of post-transplantation therapy in combination with either cyclosporin or tacrolimus. These 2 immunosuppressant agents have an identical pattern of nephrotoxicity and approximately equivalent constrictive effect on afferent and efferent renal arterioles, leading to a reduction in glomerular filtration rate (GRF) with normal filtration fraction.[11] Amphotericin B also causes arteriolar vasoconstriction, leading to renal ischaemia and decreased GFR. Clinical experience has recently suggested that administration of amphotericin B in lipid formulations may markedly diminish renal toxicity without compromising antifungal efficacy.[12] Lipid formulations are rapidly taken up by the reticuloendothelial system, leading to higher concentrations of amphotericin B in liver, lung and spleen tissue, and lower concentrations in the kidney as compared with deoxycholate amphotericin B. Therefore, the lipid formulations of amphotericin B are expected to improve the tolerability of very useful, but nephrotoxic, drug combinations such as amphotericin B plus cyclosporin or tacrolimus. Given that there are 3 lipid formulations, the potential for each of them for toxic drug interactions should be closely investigated. At this time, however, only scarce experience is available and further clinical data are needed.

1.2 Flucytosine

Flucytosine is a synthetic fluorine analogue of cytosine initially synthesised as a potential antitumour agent. Less than a quarter of the parent drug is deaminated to fluorouracil and then converted to 5-fluorodeoxyuridylic acid monophosphate, a noncompetitive inhibitor of thymidylate synthetase which interferes with DNA synthesis. Thus, concomitant administration of flucytosine with drugs like zidovudine, which are cytotoxic or suppress bone marrow function, may increase the risk of haematological toxicity. Myelosuppression attributed to the use of zidovudine is postulated to be caused by the primary intracellular metabolite of zidovudine, zidovudine monophosphate.[13-17]

Based on their differing mechanisms of action on the fungal cell, the combination of flucytosine and amphotericin B or fluconazole has been used successfully for the treatment of cryptococcal meningitis and serious candidal infections in patients with AIDS. However, flucytosine, at a dosage of 150 mg/kg/day, is in fact underused because routine monitoring of serum concentrations is warranted in almost all patients since peak serum concentrations of 100 μg/ml are associated with the development of dose-related bone marrow aplasia. Furthermore, the dosage of flucytosine must be decreased in patients with renal dysfunction, since the drug accumulates rapidly at a creatinine clearance of <75 ml/min. The use of lower dosages of 75 to 100 mg/kg/day has been recently advocated but, at this time, few data are available on their efficacy.

2. Pharmacokinetic Interactions

The term 'pharmacokinetics' covers several distinct processes: absorption, distribution, biotransformation and excretion. The involvement of these processes makes pharmacokinetic interactions more difficult to predict than pharmacodynamic interactions in terms of their clinical significance, mainly because of interindividual variability in the response.

The inhibition and, less frequently, induction of cytochrome P450 enzymes are the 2 mechanisms that underlie some of the more serious drug-drug interactions of systemic antifungals. Given that enzyme systems are located mainly in the liver and gut, the effects of enzyme induction or inhibition are most obvious when drugs are given orally because the absorbed drugs must pass through these organs prior to reaching the systemic circulation.[18-22] The majority of cytochrome P450 isoforms that primarily metabolise xenobiotics, including drugs, are encoded by 3 distinct gene fam-

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ilies, termed CYP1, CYP2 and CYP3.[23] Enzyme induction, like enzyme inhibition, is a dose-dependent phenomenon with reasonably steep dose-response relationships and therefore has clear-cut no-effect levels.[24,25]

3. Azole Antifungals

3.1 Effect of Azole Antifungals on the Metabolism of Other Drugs

The azole antifungals are known to increase the blood concentrations of various coadministered drugs up to potentially toxic amounts.[26-28] These interactions are listed in table II.

Azole antifungals inhibit the elimination of a number of drugs by competition for the enzyme CYP3A4.[23] By this mechanism, they decrease clearance and elevate blood concentrations of the affected drugs; this means that their pharmacological effects are prolonged and dose-dependent toxicity is increased.

In theory, any drug shown to be an inducer, a specific substrate or an inhibitor of CYP3A4 should have the potential to interact with azole antifungal metabolism and therefore alter the blood concentrations of azoles. However, the clinical significance of a competitive inhibition relies on: (i) relative doses of azole antifungals and the associate drug; (ii) relative bioavailability; (iii) relative affinity constants of antifungals and associate drugs for CYP3A4; (iv) interindividual variability in response to drug inducers and inhibitors (activity of CYP3A4 can vary by at least 10-fold between individual patients); and (v) the therapeutic indices of the drugs.

Among the systemic azole antifungals, ketoconazole has been shown *in vitro* to be the strongest inhibitor of CYP3A4. Itraconazole and miconazole were also potent inhibitors, although to a lesser extent, and the inhibition with fluconazole was found to be the weakest of all at equimolar concentrations.[18,27,29]

However, *in vivo* plasma free concentrations of fluconazole have been found to be 10 times greater than those of itraconazole following administration of the same oral dose,[30] because fluconazole, unlike itraconazole, is only weakly bound to plasma proteins.[31] As a result, differences in the potential of these 2 drugs for *in vivo* interactions at

Table II. Clinically significant pharmacokinetic interactions of azole antifungals: drugs whose biotransformation is inhibited and clearance decreased by concomitant administration of fluconazole, itraconazole, ketaconazole or miconazole[a]

Interactions major to life-threatening in severity: concomitant use is contraindicated
Histamine H_1 receptor antagonists: astemizole and terfenadine may induce torsade de pointes
Cisapride: this drug prolongs QTc interval which may result in torsade de pointes
Interactions major in severity
Cyclosporin: renal toxicity and neurotoxicity may be markedly increased
Felodipine: interaction documented for itraconazole
Lovastatin: interaction documented for itraconazole
Rifampicin (rifampin): interaction is documented only for ketoconazole
Rifabutin: interaction is documented only for fluconazole
Interactions moderate to major in severity
Digoxin: interactions significant with itraconazole, fluconazole and ketoconazole
Midazolam: interactions significant with itraconazole, fluconazole and ketoconazole
Triazolam: interactions significant with itraconazole, fluconazole and ketoconazole
Interactions moderate in severity
Coumarin-like drugs: anticoagulant effect is enhanced: INR should be closely monitored
Methylprednisolone: interaction significant with ketoconazole
Phenytoin: increased plasma concentration resulting in toxicity
Interactions minor to moderate in severity
Indinavir
Saquinavir
Nevirapine
Interactions minor in severity
Sulphonylureas
Chlorpropamide
Glipizide
Glibenclamide (glyburide)
Tolbutamide
Tolazamide
Zidovudine: interaction is documented only for oral daily fluconazole doses ≥400mg

a Monitor patients for signs of toxicity; interactions major in severity should contraindicate coadministration when careful monitoring of blood concentrations is not possible; adjust drug dosage regimen appropriately.

Abbreviation: INR = international normalised ratio.

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enzymatic sites are smaller than expected from *in vitro* data.

Ketoconazole has also been shown to moderately inhibit *in vitro* mono-oxygenase activities related to other forms of P450 enzyme other than CYP3A4, for example aniline hydroxylase (CYP2E1), aminopyrine demethylase (CYP1A2-2C) and debrisoquin-4-hydroxylase (CYP2D6) activities.[32]

Itraconazole is currently available as gelatin capsules containing itraconazole-coated sugar spheres. Soluble formulations using hydroxypropyl-β-cyclodextrin are currently being developed for oral or intravenous routes. These new preparations should not thoroughly modify the pharmacological properties or, more specifically the profile of itraconazole drug interactions.

3.1.1 Histamine H_1 Receptor Antagonists, Cisapride and Torsade de Pointes

Lengthening of the repolarisation and early afterdepolarisations and the propensity to block cardiac muscle K^+ channels have been proposed as a mechanism for prolonged QT interval and subsequent polyventricular tachycardia, also termed torsade de pointes. Among the clinical situations that are well established to favour the occurrence of torsade de pointes are slow underlying heart rate, lowering of extracellular K^+ levels and deleterious effect of certain drugs, for example histamine H_1 receptor antagonists and cisapride, that prolong action potential duration.

H_1 Receptor Antagonists

Second generation H_1 receptor antagonists include acrivastine (an alkylamine) cetirizine (a piperazine), and the piperidines astemizole, loratadine, levocabastine and terfenadine. Astemizole and terfenadine can cause prolongation of QT interval with resultant polyventricular tachycardia.[33-36] This arrhythmia can occur when terfenadine and astemizole are taken at higher-than-recommended dosages or in situations in which hepatic metabolism is impaired either by disease or by coadministration of drugs that inhibit P450 enzymes thought to be responsible for their metabolism. Pre-existent prolonged QT interval or significant hepatic dysfunction are risk factors. Terfenadine has been suspended in France, Greece, Luxembourg and Italy, withdrawal is planned in the US and it is now available only by prescription in the UK and Canada.

Antifungal drugs that most commonly inhibit CYP3A4-mediated terfenadine and astemizole metabolism are ketoconazole and, to a lesser extent, itraconazole. Fluconazole, which is predominantly excreted unmetabolised in the urine, has not been shown to impair the metabolism of either terfenadine or astemizole.[37-41] Itraconazole treatment has recently been shown to increase the 0 to 24h area under the plasma concentration–time curve (AUC) of astemizole from 5.46×10^{-3} to 9.95×10^{-3} mg/L·h and the 0 to infinity AUC from 17.4×10^{-3} to 48.2×10^{-3} mg/L·h and the elimination half-life of astemizole from 2.1 to 3.6 days.[42]

Although also metabolised by CYP3A4, loratadine does not appear to be associated with QT interval prolongation even when it is administered with drugs that inhibit P450 enzymes. Cetirizine and acrivastine are primarily excreted unmetabolised by the kidney and have been shown not to increase QT interval in healthy volunteers.[43]

Fexofenadine is a newly synthesised H_1 receptor antagonist and is the active metabolite of terfenadine.[44] Despite the fact that coadministered ketoconazole was shown to increase the concentration-time curve of fexofenadine in clinical trials, changes in serum concentrations remained within the range observed in controls, because only a very small percentage of the absorbed drug is converted by CYP3A4. *In vitro*, fexofenadine was shown to be 583-fold less potent than terfenadine in blocking human heart potassium channels,[35] and there were no significant changes in ECG measurements *in vivo*, in adults and children during clinical trials.[45] Nevertheless, more information is needed on the safety of fexofenadine, and studies are in progress.

Cisapride

A large number of cases of cardiac arrhythmias have been reported with antipsychotics, substituted benzamides, butyrophenones, phenothiazines and dibenzodiazepines.[46-52] Cisapride is a substituted benzamide devoid of antipsychotic activity. It is

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used therapeutically as a prokinetic agent because it stimulates gastrointestinal motility. It is metabolised by CYP3A4 (oxidative *N*-dealkylation and hydroxylation) into norcisapride. Cisapride metabolism has been shown *in vitro* to be highly sensitive to the inhibitory effect of ketoconazole, itraconazole and miconazole (and troleandomycin); fluconazole has much less effect on cisapride metabolism.[53] *In vivo*, cases of cisapride-induced long QT interval have been reported; concomitant use of cisapride with P450 inhibitors is now contraindicated.[54]

3.1.2 Coumarin-Like Drugs

The metabolism of warfarin is complex. It is extensively metabolised by multiple members of each of the 3 families of drug-metabolising P450 enzymes, and azole antifungals partly inhibit its metabolism.[55-61] The international normalised ratio (INR) should be closely monitored when azoles are started or stopped in patients receiving warfarin. The INR is the ratio of the patient prothrombin time to a control prothrombin time, that would have been obtained by a standard method using a WHO primary standard human thromboplastin:

$$INR = [PT_{pt} / Pt_{control}]^{ISI}$$

ISI = International Sensitivity Index.

Moreover, the INR should be reassessed periodically during concomitant therapy. Although inhibition occurs immediately, it is worth noting that a measurable effect on anticoagulation may not be apparent for several days because of the long half-lives of warfarin and coagulation factors. Despite the focus of this article on systemic antifungals, it is also worthwhile stressing that topical forms of azoles, which are virtually unabsorbed from intact skin, should be used with care if they are to be applied to mucous membranes, as shown by a report of a serious outcome in a patient prescribed concomitant warfarin and buccal miconazole gel.[62]

3.1.3 Cyclosporin and Tacrolimus

Cyclosporin

The major pathway for elimination of cyclosporin involves hydroxylation and demethylation by CYP3A4. Clotrimazole [50% inhibitory concentration (IC50) = 0.20 nmol/L; apparent dissociation constant of an antagonist (K*i*) = 0.15 μmol/L], ketoconazole (IC50 = 0.34 nmol/L; K*i* = 0.3 μmol/L), miconazole (IC50 = 1.74 nmol/L; K*i* = 1.30 μmol/L) and fluconazole (IC50 = 93 nmol/L; K*i* = 63 μmol/L) were shown to inhibit cyclosporin oxidase activity *in vitro* with various inhibitory potencies.[63] Azoles always induce a rapid increase in cyclosporin concentrations accompanied by deterioration of renal function and a rise in serum creatinine levels. Nephrotoxicity has been shown to be the major dose-limiting adverse effect of cyclosporin, followed by hypertension, neurotoxicity and hepatotoxicity.[29,64,65] Because the concomitant use of ketoconazole in cyclosporin-containing immunosuppressive regimens leads to the need to reduce the dose of cyclosporin by nearly 80%, and subsequent cost savings ranging from 50 to 72% during the first year after transplant, it has been proposed that ketoconazole be deliberately given with cyclosporin in fixed combination, in order to reduce drug costs in transplant recipients.[66] Whether this would also bring clinical advantages or not remains debated.[67-70] Encouraging results, however, have been recently published, showing that, in a group of 23 patients assigned to receive either cyclosporin with ketoconazole 200 mg/day or cyclosporin without ketoconazole, ketoconazole would have reduced the rate of, and delay the first episode of, rejection after cardiac transplantation.[71] In contrast, itraconazole and fluconazole increase cyclosporin blood concentrations to a lesser extent, and severe nephrotoxicity is rare.

Tacrolimus

Tacrolimus is metabolised by CYP3A4, mainly into 13-*O*-demethyl-tacrolimus in liver and gut, a biotransformation which was recently shown to be inhibited *in vitro* by ketoconazole (K*i* = 11 μmol/L) and miconazole (K*i* = 15 μmol/L). These 2 azoles are

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therefore likely to also inhibit oral tacrolimus *in vivo*, thus blood concentrations should be closely monitored and signs of tacrolimus toxicity must be watched for when these 2 agents are given concomitantly with tacrolimus.[72] In contrast, administration of tacrolimus by the intravenous route would be safer. High doses of intravenous fluconazole (400 mg/day) have been shown to slightly increase blood concentrations and decrease blood clearance of tacrolimus when given as a continuous intravenous infusion in bone marrow transplant recipients. Maximum plasma drug concentration after single-dose administration and elimination half-life of tacrolimus were increased, but not significantly, and it was concluded that no dosage adjustments are recommended for intravenous tacrolimus when administered with high-dose intravenous fluconazole.[73] Intravenous infusion of a combination of fluconazole and cyclosporin was also investigated in the same study with the same conclusion.

3.1.4 Digoxin

Digoxin is excreted for the most part unchanged. About 10% of the absorbed amount undergoes hepatic metabolism. Several case reports demonstrate that concurrent administration of itraconazole or ketoconazole and digoxin can lead to a significant elevation of digoxin serum concentrations resulting in toxicity (nausea, diarrhoea and arrhythmias).[74-76] The precise mechanism of the interaction remains unknown. Taking into account that the metabolites of digoxin are said to be active compounds, the reported cases might be explained by an inhibitory effect of itraconazole on digoxin metabolism because the interaction is clinically significant only after 9 to 13 days of concomitant treatment, although digoxin has a low therapeutic index.

3.1.5 Felodipine

Felodipine, a dihydropyridine calcium antagonist, is extensively metabolised by CYP3A4 to the inactive compound dehydrofelodipine.[77] Itraconazole greatly increases the plasma concentrations of orally administered felodipine and large interindividual differences in the extent of this interaction have been observed.[78] Although not shown in randomised trials, itraconazole probably also increases the oral bioavailability of some other dihydropyridine calcium antagonists, as suggested by a number of case reports.[79,80]

3.1.6 Lovastatin

The HMG-CoA reductase inhibitor lovastatin is a pro-drug extensively metabolised in the liver by CYP3A4 to inactive metabolites and to its active metabolite lovastatin acid. This latter step is not dependent on cytochrome P450, but the metabolism of lovastatin acid itself are CYP3A4 dependent. Itraconazole was shown to increase the concentrations of lovastatin more than 20-fold in healthy volunteers,[81] and the concentration of lovastatin acid was increased along with the concentration of lovastatin. Moreover, the plasma half-life of lovastatin acid was prolonged, probably as a result of decreased CYP3A4 activity. A case of severe rhabdomyolysis[82] has been reported, providing evidence for the clinical significance of the interaction. Moreover, interactions between CYP3A4 inhibitors and simvastatin and possibly other statins can be expected, because of close resemblances in metabolic pathways.

3.1.7 Midazolam and Triazolam

Midazolam and triazolam are CYP3A4-specific substrates. Coadministration with ketoconazole, fluconazole and itraconazole has resulted in a substantial increase of plasma concentrations of the 2 psychotropic drugs and a significant increase in sedative effects has accompanied pharmacokinetic modifications.[83,84] Although the potential of fluconazole for interactions with substrates of CYP3A4 is less than that of ketoconazole or itraconazole, recent studies have shown that fluconazole may significantly increase oral and intravenous midazolam bioavailability by inhibiting hydroxylation catalysed by CYP3A4.[85,86] In addition to hepatic CYP3A4 activity, the first-pass oxidative metabolism of oral midazolam by mucosal CYP3A4 is a major site of midazolam metabolism, which means that the magnitude of the interaction is maximal when both the inhibitor and substrate of the enzyme are given orally and simultaneously.[87]

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3.1.8 Methylprednisolone

Prednisolone and methylprednisolone are substrates and weak competitive inhibitors (K*i* = 125 and 210 μmol/L, respectively) of CYP3A4 human liver microsome enzymes *in vitro*. Ketoconazole significantly decreases the metabolism of methylprednisolone in humans through inhibition of its metabolism (clearance was decreased by about 50 to 60%) leading to observed adrenal suppression, while no significant interaction was found *in vivo* with prednisone.[88-92]

3.1.9 Oral Hypoglycaemic Agents

Sulphonylureas are extensively metabolised by the liver. Among the sulphonylureas, only glibenclamide (glyburide) has been characterised *in vitro* as behaving as a substrate/inhibitor of CYP3A4 in primary cultures of hepatocytes and liver microsomes (inhibition of cyclosporin oxidase activity with K*i* = 43 μmol/L and competitive inhibitor with 78 μmol/L).[28] *In vivo* concomitant administration of high doses of fluconazole and miconazole has been reported to increase plasma concentrations of various sulphonylureas and to expose patients to hypoglycaemic reactions, whereas low doses did not alter blood glucose levels.[93-96]

3.1.10 Phenytoin

Phenytoin is both a CYP3A4 inducer and substrate. Fluconazole and miconazole have been reported to increase trough plasma concentrations of phenytoin leading to nystagmus and ataxia. Phenytoin, in turn, induces the metabolism of itraconazole and ketoconazole, which may lead to a loss of efficacy of these drugs. In contrast, phenytoin does not seem to alter fluconazole metabolism because this azole is largely excreted unchanged.[97-102]

3.1.11 Rifabutin

Rifabutin is a rifamycin antimycobacterial agent related to rifampicin (rifampin). It is metabolised by, and also an inducer of, CYP3A4. Fluconazole significantly inhibits rifabutin metabolism *in vivo* resulting in ocular toxicity (uveitis), whereas it has no significant effect on fluconazole metabolism. In contrast, rifabutin increases the clearance of other azoles.[103-105]

3.1.12 Antiretroviral Agents

Ritonavir inhibits *in vitro* and *in vivo* the enzyme HIV-1 protease. It undergoes CYP3A4-mediated catabolism to 3 major metabolites in human liver microsomes. Ritonavir was found to be not only as potent as ketoconazole in inhibiting CYP3A4 mediated reactions, but also a potent competitive inhibitor of CYP2D6 and an inhibitor of CYP2C9/10. When used at concentrations several-fold higher than those commonly observed to induce inhibitory effects on CYP3A4 activities, ketoconazole was found to be unable to completely inhibit ritonavir P450-dependent metabolite formation. This means that the metabolism of ritonavir is likely to be only marginally altered by ketoconazole and other CYP3A4 inhibitors.[106,107]

Indinavir and saquinavir are also substrates/inhibitors of CYP3A4, although less potent inhibitors than ritonavir. This explains why the addition of ketoconazole to saquinavir has been reported to increase 3-fold the AUC of saquinavir and also the fact that there was not as large an increase in the AUC of saquinavir with fluconazole, a less potent inhibitor. Concomitant administration of indinavir with fluconazole has not led, to date, to reports of a clinically significant interaction.

Nevirapine, a non-nucleoside antiretroviral agent, is metabolised by human liver microsomes primarily via hydroxylation. It induces CYP3A4 synthesis, and enhances its own metabolism when administered long term. *In vitro* studies indicate that ketoconazole, and to a lesser extent other azoles, should elevate nevirapine blood concentrations *in vivo*, and that a nevirapine dosage reduction may need to be considered when these agents are taken concomitantly. No reports on clinical impact are currently available.[108]

Zidovudine is a thymidine analogue with antiviral activity against retroviruses. It is rapidly converted to its 5′-*O*-glucuronide metabolite. Drugs that inhibit glucuronidation, such as azoles, increase the bioavailability of zidovudine and may thus increase the risk of myelotoxicity. Concomitant high doses of fluconazole significantly elevate zidovudine blood concentrations *in vivo*.[10,109]

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Table III. Agents that may alter azole antifungal (fluconazole, itraconazole, ketoconazole, miconazole) metabolism

Main features
Pharmacokinetic in nature
Blood concentrations of azoles are decreased
The pharmacological effects (therapeutic and toxic) of the azole are modified
This may result in a loss of the efficacy of the azole
Drugs that induce the metabolism of azoles
Carbamazepine and phenobarbital (phenobarbitone): case reports involve only itraconazole
Phenytoin: case reports involve itraconazole and ketoconazole
Rifampicin (rifampin): case reports involve all 4 azoles; azoles and rifampicin should not be administered concomitantly
Interactions moderate in severity and are dose-dependent
Patients should be monitored for efficacy and the azole dose should be adjusted appropriately
Drugs that decrease gastrointestinal absorption of azoles
Antiacid and cytoprotector agents, didanosine: case reports involve itraconazole and ketoconazole. Interactions are minor to moderate in severity; azoles must be taken 2 hours before the administration of these drugs and patients should be monitored for efficacy

3.1.13 Antidepressant Drugs

Imipramine, a tricyclic antidepressant drug, is *N*-demethylated in the liver to the active metabolite desipramine, a metabolic pathway which is mediated by at least 3 different isoforms: CYP1A2, 2C9, 2D6 and 3A4. Very recently, the role of CYP3A4 in the metabolism of imipramine has been further characterised showing that ketoconazole is responsible for partial inhibition of *N*-demethylation, which leads to a prolongation of about 20% in imipramine half-life. This interaction, however, does not seem to be clinically significant. In contrast, fluconazole has been shown to significantly inhibit the metabolism of nortriptyline.[110,111]

3.2 Agents That May Alter Azole Antifungal Metabolism

Drug interactions with azoles can also occur through induction of P450 isoenzymes, which leads to an increase in their clearance by accelerating their metabolism. This increase of drug clearance decreases the efficacy of azoles. Drugs known to produce a clinically significant decrease in blood concentrations of azoles are listed in table III.

3.2.1 Barbiturates, Carbamazepine, Phenytoin and Rifampicin (Rifampin)

Barbiturates, carbamazepine, phenytoin and rifampicin are some of the few drugs that have been noted as inducing the metabolism of concomitant drugs at therapeutic concentrations in humans, by increasing the amount of CYP3A4 in the microsomes. Concomitant administration of these drugs mainly induces the metabolism of ketoconazole, itraconazole and miconazole, and to a lesser extent that of fluconazole. However, cases of recurrence of infection during antifungal therapy have been reported when rifampicin was coadministered with fluconazole, which has been explained by a decrease in AUC and half-life of the antifungal.[112-119]

3.2.2 Isoniazid

Isoniazid is a probe drug for detecting *in vitro* metabolising enzyme *N*-acetyl transferase, and it has been shown that long term isoniazid therapy may induce CYP2E1 expression. Despite the fact that hepatic enzyme induction of CYP3A4 has never been noted with isoniazid, this drug has been proposed as having the potential to significantly induce the metabolism of ketoconazole and other azoles. This proposal is based on a report of 2 cases in which isoniazid, rifampicin and ketoconazole were coadministered and a marked decrease in rifampicin and ketoconazole concentrations were observed. No clear conclusions were actually drawn by the authors of the report as to the role of isoniazid in the decrease in rifampicin and ketoconazole concentrations.[120,121]

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3.3 Interactions that Occur During Gastrointestinal Absorption

Interactions at the absorption site may alter the bioavailability of azole antifungals. These interactions are listed in table III.

3.3.1 Antiacid, Cytoprotector Agents and Didanosine

Recent studies have demonstrated that the gastric dissolution and subsequent absorption of ketoconazole and itraconazole in humans are dependent on low gastric pH (pH <4), and that their bioavailability is significantly reduced by concomitant administration of drugs that increase gastric pH such as H_2 receptor antagonists (cimetidine, ranitidine, famotidine), proton pump inhibitors, sucralfate (a weak base aluminium salt) and didanosine (the various forms of which are buffered in order to increase absorption and contain both aluminium and magnesium). Absorption of ketoconazole and itraconazole may thus be significantly reduced by the concomitant use of these agents. In contrast, and theoretically, the bioavailability of fluconazole is not affected when gastric acidity is decreased, and this has been confirmed by clinical data showing that although cimetidine was found to slightly reduce AUC and the time to reach peak or maximum concentration following drug administration (t_{max}) of fluconazole, there were no clinical consequence. Aluminium and magnesium hydroxide were also shown not to interfere with fluconazole absorption.[122-129]

4. Non-Azole Antifungals

4.1 Griseofulvin

Griseofulvin undergoes extensive hepatic metabolism and is an enzymatic inducer of coumarin-like drugs and oral contraceptives.[63,65] Adjustment of the dosage of oral anticoagulants may be required during concomitant griseofulvin therapy and after griseofulvin has been withdrawn.[130] Griseofulvin also has the potential for inducing the metabolism of endogenous and exogenous estrogens thereby leading to loss of efficacy of contraceptives and even menstrual irregularities.[131]

4.2 Terbinafine

Terbinafine is commonly used as a topical antifungal, but it is also available in Europe as a systemic antifungal given by the oral route. Unlike azole antifungals, terbinafine is weakly bound to hepatic cytochromes and its metabolism involves only about 5% of the metabolising capacity of hepatic P450 enzymes. Thus, it should not alter the disposition of other drugs metabolised via these enzyme systems, and actually has a low potential for drug-drug interactions.[63,65] However, in healthy volunteers, elimination of terbinafine has been shown to be decreased by coadministration of cimetidine 400mg twice a day and increased by 6 days' pre-treatment with rifampicin 600 mg/day. Based on this study, a warning regarding the rifampicin/terbinafine interaction is included in the label of the product, but no case reports of this interaction can be found in the literature.[132,133]

5. Conclusion

In contrast with amphotericin B and flucytosine, interactions involving azole antifungals consist largely of the processes of enzyme inhibition and enzyme induction. In our opinion, the 1990s have witnessed 4 marked changes in the treatment of fungal infections: (i) the introduction of fluconazole and itraconazole, the latter being a potent inhibitor of CYP3A4; (ii) the introduction of less nephrotoxic, lipid-containing formulations of amphotericin B, which are expected to ultimately replace the current formulations; (iii) the results of a recently published comparative trial showing that coadministration of ketoconazole not only reduces the dosage of cyclosporin required, which is not new, but would also reduce the rates of rejection and infection, without persistent toxic effects, which is new;[72] and (iv) the development of controlled pharmacokinetic studies, which have established that, in addition to the liver, the gut wall also contributes extensively to the first-pass metabolism of drugs which are CYP3A4 substrates. It has been comprehensively established that there are large interindividual differences in the liver content and

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catalytic activity of CYP3A4.[26] Moreover, it has been shown that intraindividual hepatic and intestinal CYP3A4 activities do not correlate well, which results from a lack of correlation between the concentration of CYP3A4 mRNA and that of CYP3A4 protein in the intestine.[134]

Therefore, whereas blood and tissue concentrations of CYP3A4 inducers or inhibitors are major parameters for the extent of interactions, interindividual differences in the CYP3A4 activities in liver and gut are responsible for the large interindividual variations observed in the extent of azole interactions at enzymatic sites *in vivo*. Furthermore, this also explains why one cannot precisely extrapolate the extent of these interactions *in vivo* in particular patients from data obtained *in vitro* in standardised models. However, when potent inhibitors of CYP3A4 (for example ketoconazole and itraconazole) are shown to increase the bioavailability of a drug, it can be reasonably extrapolated that these agents would act in the same manner on the kinetics of other drugs inside the pharmacotherapeutic group, if these drugs undergo the same metabolic pathway.

Recent pharmacokinetic studies have also shown that one cannot expect to easily avoid a potentially serious interaction by simply increasing the ingestion time interval between the drugs. As an example, when itraconazole and felodipine[78] or itraconazole and triazolam[135] have been coadministered, pharmacokinetically significant interactions are observed even when felodipine or triazolam are ingested 24 hours after itraconazole, because the inhibitory effect of the latter drug has been shown to last at least for 24 hours.

Finally, it appears that there is no other key to the safe combined administration of drugs that extensively interact with azoles at CYP3A4 sites, than to monitor patients for signs of toxicity or loss of efficacy, to adjust doses accordingly, and at least in our opinion, to *contraindicate* the combinations when the monitoring of blood concentrations is not possible and serious adverse effects may ensue.

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