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Managing drug interactions in the patient with aspergillosis

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Drug interactions are a common and recurring problem in immunocompromised patients with aspergillosis. While the introduction of new antifungals has expanded opportunities for lowering drug toxicity, virtually all antifungal regimens still carry the risk for pharmacokinetic and pharmacodynamic interactions. Drug interactions affecting the pharmacokinetics of antifungals used in the treatment of aspergillosis, or interactions that decrease the metabolism/elimination of a drug with a narrow index for efficacy (e.g. anti-retroviral therapy) or safety (e.g. immunosuppressants, chemotherapy) have the greatest potential to cause serious harm. Additionally, azole-based treatment regimens for aspergillosis carry a risk for uncommon, but potentially life-threatening, interactions that affect cardiac conduction leading to severe tachyarrythmias such as Torsades des Pointes. Clinical diagnosis of antifungal drug interactions in immunocompromised patients remains a challenge, as adverse sequelae are often masked by infection or other drug therapies (especially chemotherapy). Therefore, a high index of suspicion and a proactive, multidisciplinary approach is essential for preventing drug interactions in patients with aspergillosis. Improvements in laboratory support (i.e. patient pharmacogenetic profiling, expanded use of serum drug level monitoring) will become increasingly important for managing drug interactions patients on complex treatment regimens.

Keywords Drug interactions, cytochrome P-450, azoles, polygene, echinocandins, adverse effects

Introduction

Drug interactions remain one of the most common, recurring challenges associated with the safe and effective management of *Aspergillus* infections. Factors that can increase the risk for clinically-significant drug interactions include advanced age, chronic illness, renal or hepatic dysfunction, polypharmacy, and receipt of medications with a narrow therapeutic index or requirement for therapeutic drug monitoring [1]. Because many of these risk factors are common among patient groups at highest risk for developing opportunistic fungal infections (e.g. transplant, hematological malignancy, acquired immune deficiency syndrome, etc.), drug interactions should be anticipated in any patient receiving systemic antifungal therapy for aspergillosis.

Systemic antifungal therapy used in the treatment of *Aspergillus* infections can interact with a wide range of medications leading to potentially severe adverse effects. Historically, these interactions were unavoidable due to the limited treatment options (amphotericin B, itraconazole) or accepted as part of the risk of treating a life-threatening infection when no other treatment options were available. However, the introduction of a new class of antifungals (echinocandins), lipid amphotericin B formulations with reduced nephrotoxicity, and broader-spectrum triazoles (voriconazole, posaconazole) now provides for greater flexibility for treating aspergillosis while minimizing the risk for adverse effects. Many of these newer antifungals still interact with a number of medications through a variety of pharmacokinetic and pharmacodynamic mechanisms

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[2]. Therefore, knowledge of drug interaction profiles for antifungal therapies is essential for tailoring antifungal therapy in the medically-complex patient.

Mechanisms of antifungal interactions

A drug interaction occurs when the pharmacokinetics or pharmacodynamics of a drug in the body are altered by the presence of one or more interacting substances [1]. While drug interactions are often described between two drugs, multiple interactions are possible with the polypharmaceutical regimens frequently encountered in the patient with aspergillosis. Other than drug–drug interactions, drugs may interact with food, nutrients including vitamins and minerals, alternative medicines (i.e. herbals, homeopathic remedies), drug formulations (e.g. excipients), inflammatory states (cytokines) or environmental factors [1]. Various disease states including renal and hepatic insufficiency can prolong or enhance the magnitude and duration of the interaction. Pharmaceutical or physical incompatibilities of drugs *ex vivo*, which manifest when drugs are combined as admixtures for IV infusion, are occasionally described as *drug interactions* although these interactions are conceptually and mechanistically distinct from interactions that occur inside the body.

The majority of drug interactions involving systemic antifungal therapy used in the treatment of aspergillosis occur in the gut, liver or kidney and are pharmacokinetic in nature, resulting in changes in the absorption, distribution, metabolism or excretion of the interacting drug as well as the antifungal agent [2]. In the gastro intestinal (GI) tract, changes in pH, complex formation with ions, or interference with transport and enzymatic processes in the intestinal lumen can interfere with drug absorbance. Induction or inhibition of metabolism in the liver can inhibit or accelerate, respectively, drug clearance from the body. In the kidney, decreases in glomerular filtration, active tubular secretion or other mechanisms can slow renal elimination resulting in excessive drug exposure [3].

Antifungal interactions in the GI tract

Older azoles antifungals are particularly susceptible to pharmacokinetic drug–drug interactions in the GI tract. Ketoconazole and itraconazole are weak bases, virtually insoluble in water, and are ionized only at a low pH. Consequently, dissolution and absorption of these compounds is heavily dependent on acidic gastric conditions in the stomach [4,5]. Drugs that increase gastric pH (e.g. H_2 antagonists, proton pump inhibitors) can slow the dissolution of the solid dosage forms and decrease drug available for absorption in the intestinal lumen. Antacids, metal ion containing drugs (e.g. sulcralfate), and vitamin supplements can also slow dissolution through binding or chelation interactions that impair transport of the drug across the intestinal epithelium [2,6,7]. Pharmacokinetic studies in healthy volunteers have documented 30–60% reductions in serum itraconazole concentrations (C_{max}, AUC_{0-24}) when itraconazole capsules are administered with either famotidine or omeprazole [8,9]. Unlike the capsule formulation where absorption is maximal under acidic conditions and a fed state, absorption of itraconazole in cyclodextran solution is not significantly affected by gastric pH changes and is maximal under fasted state [10]. Similarly, the dissolution of voriconazole is not affected by gastric pH, although co-adminstration of the drug with fatty foods can reduce its bioavailability by 10% [11]. Posaconazole, which shows chemical similarity to itraconazole (pk_a 3.6–3.7) but slightly improved aqueous solubility at a pH <7 (posaconazole log P-3 vs. itraconazole log P-5.66), is currently available in Europe as an oral suspension that is administered with food, or in divided doses (two to four times daily) to maximize absorption. Unlike itraconazole, increases in gastric pH or co-administration with antacids does not appear to significantly reduce the absorption of posaconazole [12]. However, cimetidine does reduce posaconazole exposure by 40%, when given concurrently or sequentially (prior to posaconazole) in healthy volunteers [12–14]. The mechanism by which cimetidine reduces posaconazole exposure is currently unknown.

In the intestinal lumen, two mechanisms are known to play an important role pre-systemic drug clearance or alter drug absorption. The first mechanism is P-glycoprotein (P-gp) – a versatile drug transporter found on the apical plasma membrane surface of enterocytes that functions as a 'detoxification' pump that expels drug back into the intestinal lumen (Fig. 1) [15]. Azoles such as ketoconazole or itraconazole can be both substrates and inhibitors of the P-gp. Initial P-gp efflux of azoles into the intestine can be inhibited after several days of therapy resulting in improved bioavailiblity [16]. Similar patterns have been reported for some azoles when administered orally with grapefruit juice, which acts as an inhibitor of intestinal P-gp and CYP 450 [16,17]. Although voriconazole and posaconazole have not been shown to be major substrates or inhibitors of P-gp, some interaction is likely given the CYP3A4 inhibition profile of these agents and the overlapping substrate specificity of P-gp and the CYP3A4 isoform [16,17].

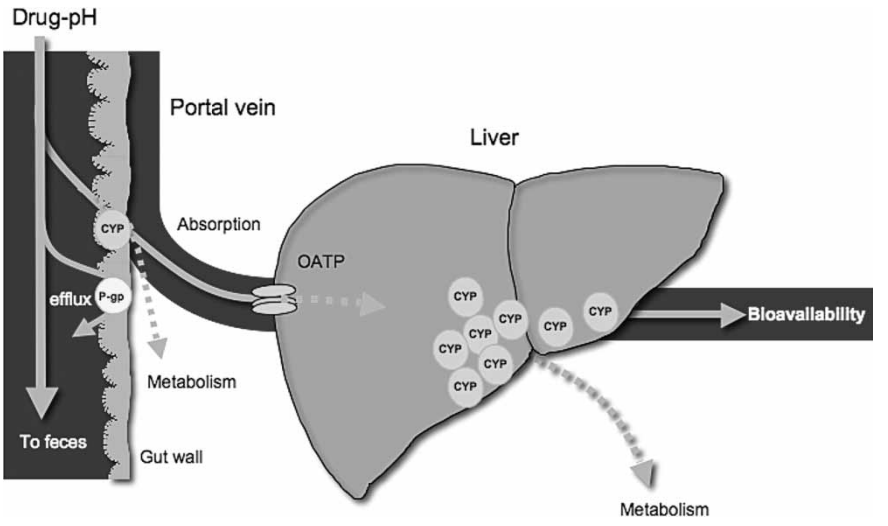

Fig. 1 Pre-systemic clearance and metabolism of antifungal compounds. P-gP, P-glycoprotein; CYP, cytochrome P-450 enzyme. Arrows represent drug pathways for pre-systemic clearance or metabolism.

An overlapping mechanism of pre-systemic clearance of azole antifungals involves intestinal metabolism of lipophilic molecules by the cytochrome P450 (CYP)3A4 enzymes, which result in inactive and active metabolites [18]. Similar to P-gP, some triazole antifungals are both substrates and inhibitors of CYP3A4 suggesting that P-gP and CYP3A4 work in a coordinated fashion to prevent the absorption of xenobiotics. The degree of intestinal CYP3A4 differs from patient to patient and is not under coordinate expression of CYP3A4 in the liver, which is the principal site of drug metabolism and (presumably) clinically significant interactions affecting drug metabolism [18].

Antifungal interactions involving drug metabolism

The principal site for drug metabolism is the liver where lipophilic compounds are transformed into ionized metabolites for renal elimination. This transformation or metabolism generally occurs via two different types of reactions: (i) Phase I (non-synthetic) reactions, which include oxidation, reduction and hydrolysis, and (ii) Phase II (synthetic) reactions resulting from conjugation with other molecules (e.g. glucoronidation, sulfation) to improve aqueous solubility [1,2]. Interference of drug metabolism through these pathways by induction, suppression, or inhibition of drug metabolism accounts for some of the most common and potentially severe drug interactions encountered in the clinic.

Phase I oxidative reactions are an important mechanism for biotransformation of azole antifungals [2]. Most oxidative reactions are catalyzed by a superfamily of mixed-function mono-oxygenases called the cytochrome P40 system. Although 14 human families of CYP enzymes have been identified, 95% of all drug oxidation occurs through the action of six CYP enzymes: CYP1A2, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 [1]. CYP3A4 is the isoform most frequently associated with severe drug interactions due to its involvement in the metabolism of 60% of all oxidized drugs (Table 1) [1]. In terms of drugs used in the treatment of aspergillosis, itraconazole, and voriconazole undergo extensive Phase I metabolism by CYP3A4 and 2C19, respectively. On the other hand, posaconazole, is eliminated by UDP glucoronidation – a phase II mechanism that results in predominantly billiarly/ fecal excretion [19].

Considerable variability in CYP enzyme activity may be observed between patients due to medical, environmental, and dietary factors [18,20,21]. Additional variability in oxidative metabolism arises from genetic polymorphisms (non-random genetic mutations) that

Table 1 Interaction profiles of azole antifungals

Drug	CYP3A4	CYP3A4	CYP2C8/9	CYP2C8/9	CYP2C19	CYP2C19
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate
Fluconazole	++		++		+	+
Itraconazole	+++	+++	+			
Voriconazole	+	+	++	+	++	+++
Posaconazole	++					

can be found in subpopulations of patients for specific CYP enzymes. Specifically, clinically-significant genetic polymorphisms in CYP metabolism have been described for CYP2D6, CYP2C9, and CYP2C19 [1]. The frequency of these polymorphisms differs substantially among different racial backgrounds. Unlike the unimodal population distribution of CYP3A4, 15–30% of the Asian population and 3–5% of caucasions are poor metabolizers at CYP2C19. Polymorphisms in CYP2C19 metabolism have been linked to differences in the pharmacokinetics of voriconazole among various ethnic groups [22]. Patients who are homozygous poor metabolizers through the CYP2C19 pathway may experience, on average, fourfold higher serum concentrations of voriconazole compared to heterozygous extensive, or homozygous extensive metabolizes (majority of the population) receiving equivalent [22].

CYP-mediated metabolism is governed by several factors including the physiochemical properties of the drug (lipophilicity), and drug pharmacokinetics. Because ketconazole and itraconazole are highly lipophilic, their clearance is heavily dependent upon metabolism through several CYP 450 pathways including CYP3A4. Fluconazole, on the other hand, is relatively less lipophilic and requires less CYP transformation at lower dosages ($<$200 mg/d) for clearance from the body [2]. Co-administration of azoles with drugs that induce or accelerate strongly CYP-450 metabolism, particularly CYP3A4, can result in low [23] or undetectable levels of the azole antifungal [24,25]. Higher antifungal dosages (particularly of ketoconazole, itraconazole, voriconazole, posaconazole) cannot overcome this interaction.

All azoles are also reversible inhibitors of CYP enzymes in humans [2]. This inhibition is probably a collateral effect of their mechanism of antifungal activity, namely inhibition of 14-alpha-demethylase- a CYP P450 enzyme in fungi involved in the biosynthesis of ergosterol (Fig. 2). Once again, the degree and type of inhibition varies with each azole on the basis of its physiochemical characteristics and pharmacokinetics. The most important drug interactions seen with azole antifungals typically arise from inhibition of CYP3A4, which plays a central role in the metabolism of a broad array of drug therapies used for cardiovascular disease, endocrine disorders including hyperglycemia, anaesthesia, psychiatric disorders, epilepsy, cancer chemotherapy, immunosuppression used in transplantation, and treatment of infectious diseases. A general overview of interactions associated with antifungal therapy are presented in Table 2.

Antifungal interactions involving drug transporters

Organic anion transporting polypeptides (OATP) represent a group of membrane carriers that transport a wide spectrum of amphipathic substrates. Currently nine OATPs have been identified in humans and are expressed in various tissues including the liver, blood brain barrier, choroids plexus, lung, heart intestine, kidney, placenta and testes [26]. Collectively, OATPs transport a variety of diverse compounds and function as uptake transporters that facilitate the influx of compounds [26]. The OATP family appears to play a major role in hepatobilliarly drug extraction as they are prominently located on the basolateroal (sinusoidal) membranes of hepatocytes [26]. The echinocandin caspofungin has recently been reported to be a substrate of the OATP-1B1 (OATP-C) transporter [27]. This may explain in part why caspofungin exhibits

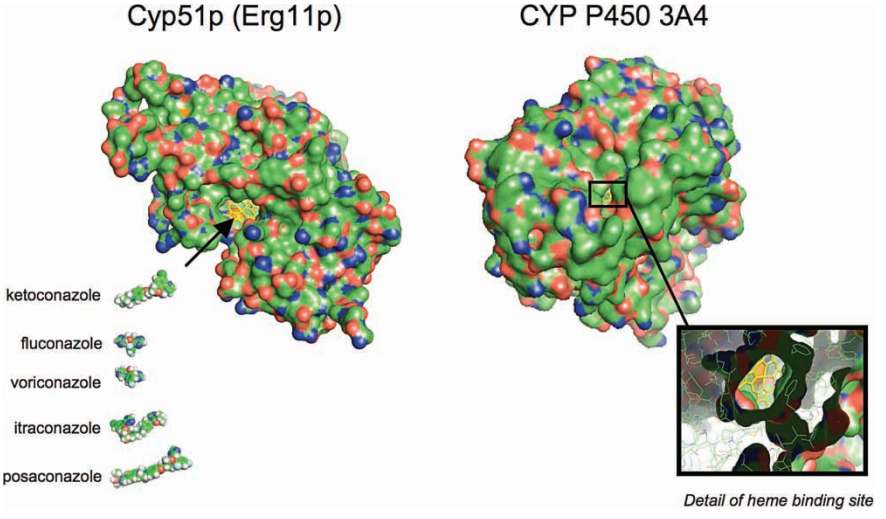

Fig. 2 Comparison of the three-deminisional structure and target binding site of the fungal cytochrome P450 14-alpha demethylase (CYP 51p) and human cytochrome P450 3A4 isoenzyme. Putative structure of CYP 51p basee on crystal structure of homologous *Mycobacterium tuberculosis* P450 14-alpha demethylase.

Table 2 Summary of common antifungal interactions in patients with aspergillosis

Azole +	Carbamazepine
Cytochrome P450 inducers	Phenobarbital
	Phenytoin
	Isoniazid
↓ Azole concentration	Rifampin
	Rifabutin
	Nevirapine
Azole +	Statins
Cytochrome P450 substrates	Cyclosporine
	Tacrolimus
↑ Substrate concentration	Sirolimus
	Protease inhibitors (saquinavir, ritonavir) [Ca^{2+}] channel blockers (diltiazem, verapamil, nifedipine, nisoldipine)
Caspofungin +	
Cytochrome P450 inducers	Rifampin
	Other inducers?
↓ Caspofungin concentration	
Caspofungin +	Cyclolsporine (increase caspofungin AUC 30%)
OATP substrates?	Tacrolimus (decrease tacrolimus AUC 20%)
↑↓ Mixed effects	
Micafungin +	Nifedipine
OATP substrates?	Sirolimus
↑ Substrate concentrations	Cyclosporin

modest interactions with cyclosporine (increased caspofungin AUC 35%) and rifampin (decreases caspofungin AUC by 30%) despite lack of substrate or inhibitory activity in human CYP3A4 enzymes [27]. Similarly, caspofungin can decrease tacrolimus concentrations by 20%; although OATP mechanisms have not been linked with this interaction. Currently, additional work is underway to identify the precise roles and substrate specificity of various OATPs in the liver and other tissues in humans.

Antifungal interactions involving renal elimination

Decreases in renal function can result in decreased clearance of renally eliminated drugs, accumulation, and enhanced toxicity if dosages are not appropriately modified. Amphotericin B-induced nephrotoxicity is frequently exacerbated by other drugs that cause damage to the distal tubules of the kidney (i.e. cyclosporine, tacrolimus, aminoglycosdies, cisplatnin) [2,3]. Electrolyte disturbances that accompany distal tubular damage (hypokalemia, hypomagnesiunemia) can also be enhanced by other medications (i.e. loop and thiazide diuretics, corticosteroids), or augment the pharmacological effect of drugs such as antiarrythmics, non-depolarizing skeletal muscle relaxants, and digoxin with harmful results. Because of their effects on salt/water retention, corticosteroids can enhance amphotericin B-induced hypokalemia and contribute to cardiomyopathy [28]. Therefore, this combination should be avoided in patients with poorly-compensated congestive heart failure [28].

Drug interactions that arise from amphotericin B-associated nephrotoxicity are unavoidable in patients with aspergillosis. Therefore, management of these interactions focuses on preventative measures to limit the severity of the reaction, and careful monitoring and supplementation of electrolyte deficiencies. Lipid formulations of amphotericin B should be substituted for amphotericin B deoxycholate whenever possible in patients with underlying renal dysfunction or concomitant nephrotoxic agents. Hydration with normal saline before and after amphotericin B infusions may also be helpful for blunting tubular-glomerular feedback mechanisms that intensify decreases in glomerular filtration [3]. Careful monitoring of renal function (serum creatinine, blood urea nitrogen (BUN) and electrolytes (i.e. K+, Mg++ and PO_4) is essential in aspergillosis patients receiving amphotericin B-based therapy. Blood or serum concentration monitoring of renally-eliminated drugs such as the aminoglycosides, cyclosporine, and tacrolimus require close monitoring even in the absence of reduced glomerular filtration, as changes in blood or serum concentration of these drug frequently precede changes in the serum creatinine [2].

Drug interactions involving cardiac conduction

Although cardiac toxicity is a relatively uncommon adverse effect of antifungal therapy, it is potentially the most severe sequela of drug–drug interactions in the patient with aspergillosis. In the United States alone, between 300 000 and 400 000 people die annually of sudden cardiac death [29]. In some cases, this sudden cardiac death is the result of a polymorphic ventricular tachyarrythmias called Torsades de Points (TdP) that can be induced either directly or indirectly by drug therapy including antifungals used in the treatment of aspergillosis. Prolongation of the QT interval, an indication of delayed cardiac repolarization, has been demonstrated to play a key role in drug-induced TdP. The drug-related mechanism thought to be responsible for drug-induced QT prolongation is blockade of the human ether-a-go-go (HERG) gene product that encodes a rapid component of the delayed rectified potassium channel (I_{kr}). The blockade of HERG encoded I_{kr} results in accumulation of potassium within the myocyte, which, in return, delays cardiac

repolarization [30]. Electrical instability that occurs during this repolarization phase may abruptly reverse its course resulting in an early after polarization event that triggers a second action potential that spreads to the ventricles resulting in a premature ventricular complex (PVC) on ECG. If the pathological process is repetitive or self-sustaining, the polymorphic ventricular arrhythmia TdP can develop leading to syncope, dizziness, palpitations or sudden death [30].

While modest increases in the Qtc interval are common with many drug therapies, TdP is uncommon outside of patients with pre-existing cardiac conduction abnormalities [30]. The extent of QT-interval prolongation that develops on drug therapy can be influenced by a number of drug-related and host-specific risk factors. Drug-related factors that can influence the risk of TdP include the intrinsic QT prolongation potential of the drug itself (ability to inhibit I_{kr} at physiologically-relevant concentrations), co-medications associated with QT-prolongation, metabolic drug interactions particularly those involving CYP3A4 that result in supratherapeutic concentrations of a second-co administered drug known to inhibit I_{kr}, drug dose, and route of administration (intravenous (IV) > oral) [30]. Host specific factors include electrolyte derangements (hypokalemia, hypomagnesiunemia, hypocalcemia), increased age, female gender, underlying structural heart disease (mycocardial infarction, congestive heart failure), bradycardia, underlying organ dysfunction with failure to adjust dosage accordingly for drugs known to prolong the QT interval, hypothyroidism, central nervous system tumor or infection, and obesity [30]. More recently, genetic predisposition has associated with inherited long-QT syndrome as well as drug-induced TdP [31,32]. Mutations in genes involved in cardiac repolarization may result in symptomatic or asymptomatic decreases in cardiac repolarization reserve that can remain clinically silent until a pharmacological stimulus is added, thus unmasking the cardiac ion mutation resulting in symptomatic arrhythmias. Both, ketoconazole and fluconazole have been implicated with cases of TdP in patients with clinically asymptomatic long-QT syndrome [30].

Although current antifungals used in the treatment of invasive aspergillosis (IA) have shown minimal HERG inhibition at clinically achievable levels, direct I_{kr} inhibition cannot be excluded at high drug exposures [30]. In pre-clinical testing of voriconazole, high-dosages administered to dogs resulted in arrhythmias, PVCs, and prolonged QT intervals [33]. In placebo-controlled Phase I studies, the effect of voriconazole was measured in healthy volunteers following single and multiple doses. Measurement of the corrected QT-interval revealed 28% of patients with QTc intervals elevated ≥ 30 ms above baseline but < 60 ms, compared to 19% in the placebo group. One sudden death was also reported in phase III studies as a result of cardiac arrest following voriconazole administration, although the patient had multiple risk factors including hypokalemia and prior history of benign ventricular arrhythmias [33].

A more common scenario for antifungal therapy-associated QT-prolongation is through the inhibition of CYP P450 metabolism of drugs with more potent effects on myocete I_{kr} channels [30]. Case-reports of antifungal-associated TdP most commonly result from combinations of either ketconazole or itraconazole with terbinafine, astemizole, cisapride, or quinidine derivatives. These drugs should be considered contra-indicated in any patient receiving itraconazole, voriconazole or posaconazole. Any patient receiving azoles should be monitored for dosage adjustments, potential drug interactions, and electrolyte disturbances to minimize the possibility of a proarrhythmia [30]. Avoidance of azoles may be prudent, when possible, in any patient will poor repolarization reserve (i.e. inherited long QT-syndrome).

Managing clinically-significant interactions in patients with aspergillosis

While all drug interactions may not be clinically significant, those affecting the pharmacokinetics of antifungals used to treat *Aspergillus* infection, or interactions that decrease the metabolism/ elimination of a drug with a narrow index for efficacy (anti-retroviral therapy) or safety (immunosuppressants, chemotherapy) have the potential for serious harm to the patient (Table 2). Importantly, many of these interactions may go undetected unless clinicians adopt a proactive approach towards identifying these potentially serious drug interactions in patients on multiple medications. Patients with IA are often critically ill, immunosuppressed, with multiple co-morbidities and compromised renal and hepatic function. As a result, subtle clues or early indicators of drug toxicity (e.g. electrolyte disturbances, increases in liver function tests) are often missed or attributed to other factors including infection. Adverse drug reactions should be considered in any patient with unexplained changes in renal or hepatic function or cognitive disturbances. CNS toxicities in particular, can arise with excessive cyclosporine or tacrolimus exposure following the initiation of azole therapy and cannot necessarily be ruled out by 'normal therapeutic' serum drug concentrations of the immunosuppressive agent [34].

Table 3 Recommendations for serum level monitoring of antifungals

Agent	Justified in select situations?	Target range	Timing of sample
Amphotericin B	No	N/A	N/A
Flucytosine	Yes – toxicity	<100 mcg/mL	2 h post-dose peak
Fluconazole	No	N/A	N/A
Itraconazole	Yes – ensure absorption, efficacy	>0.5 mcg/mL	Trough after seven days of therapy
Voriconazole	Yes – variable metabolism associated with sub-therapeutic and toxic concentration drug interactions, pediatrics?	1–2 to 6 mcg/mL	Trough after seven days of therapy
Posaconazole	Yes, ensure absorption, efficacy	>0.25 mcg/mL?	Trough after seven days of therapy

In some patients, a trial switch to alternative antifungal agents with a non-interacting drug or holding doses of the interacting medication may be the only available option for managing a suspected interaction. Other steps for preventing or minimizing the effect of the interaction include: (i) avoiding one or more of the interacting drugs, (ii) substitution of one of the drugs with a non-interacting drug, (iii) staggering the time or modifying the dose strength or interval of drug administration, (iv) changing the route of administration, and/ or (v) more intensive monitoring for drug serum levels or toxicity.

Laboratory support is essential in the management of drug interactions in patients with aspergillosis. Beyond routine electrolyte and serum drug level monitoring of agents with a narrow therapeutic index, measurement of antifungal serum drug concentrations, in select situations can provide useful information concerning inadequate drug exposures [35]. Typically, four criteria must be fulfilled to justify the use of serum drug concentrations to guide drug dosing or suspicions of antifungal interactions: First, an assay with appropriate sensitivity, specificity and 'turnaround time' from the clinical laboratory must be available for analysis of the drug in question. Second, the clinical efficacy or toxicity of the drug must be delayed or difficult to directly measure. Third, the drug must exhibit significant inter-patient variability in pharmacokinetics to an extent that drug concentrations cannot be assumed from empirical dosing strategies. The fourth requirement (and often most problematic) is that a correlation must be established between drug concentrations and clinical efficacy/ toxicity.

Although antifungal therapy does not typically fulfill all four criteria, monitoring in select situations may be helpful for certain agents where non-compliance, drug interactions, or unexpected toxicity is encountered (Table 3) [35]. For example, measurement of a single trough concentration once the patient reaches steady state (i.e. seven days of therapy) of an azole-antifungal can verify sub-therapeutic antifungal concentrations in the serum resulting from drug interactions that induce cytochrome P450 3A4. Serum drug level monitoring may be especially important in patients where there is concern for adequate drug bioavailability. Equally important is the monitoring that is required once the azole antifungal therapy is stopped, as many patient will persist with subtherapeutic levels after the P450 inhibition effect of azoles is lost. Serum drug monitoring is most frequently indicated for flucytosine, itraconazole, and occasionally voriconazole and posaconazole. TDM for other antifungals is more difficult to interpret and apply to clinical dosing. A summary of current approaches for antifungal serum drug monitoring is presented in Table 3.

An important future goal of laboratory testing would be to have a rapid, reliable test capable of detecting patient genetic factors that can predispose to severe drug interactions or cardiac toxicity with antifungal therapy. Recently, Roche pharmaceuticals was granted a license for the first pharmacogenomic microarray test to detect common polymorphisms in the 2D6 and 2C19 genes, which play a role in the metabolism of about 25% of all prescription drugs including voriconazole. The Affymetrix chip costs roughly US$500 per test, and is still in the early phase of clinical implementation. Therefore, it may not be a cost-effective tool for determining a patient's risk for a severe drug interaction. However, in the not too distant future, patients undergoing cancer chemotherapy or solid organ/ hematopoietic cell transplantation will likely receive a CYP-450 work-up at baseline that will be reviewed along with current medications, renal, and hepatic function to individualize safe and effective therapy for aspergillosis infections.

Conclusions

Patients with IA have many risk factors for experiencing potentially harmful drug interactions. Although some drug interactions may be trivial or have minor effects, interactions that enhance the metabolism of antifungals used to treat *Aspergillus* infection, interaction that affect drugs with a narrow therapeutic index

(i.e. immunosuppressants, chemotherapy, antiretrovirals), and interactions that increase cardiac QT-prolongation should always be considered important and managed in a proactive fashion. New treatment options and expanded opportunities for laboratory support, including therapeutic drug monitoring and pharmacogenomic assessment that will allow clinicians to stratify a patient's risk for drug adverse effects and drug interactions, will become increasingly important tools in the management of drug interactions in patients with aspergillosis.

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