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Resident's Page

Drug interactions of azole antifungals

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ABSTRACT

Drug interactions can occur when two or more medications are simultaneously given, and one drug increases or decreases the effectiveness of the other. Azole antifungal agents show a wide range of interactions with other drugs. Failure to recognize a drug–drug interaction may produce harm to the patient, including enhanced toxicity of the concomitantly administered medication. Most of the interactions of azole antifungals are of pharmacokinetic type. This article reviews the clinically relevant drug interactions of commonly used antifungals - fluconazole and itraconazole.

Keywords: Fluconazole, Itraconazole, Drug interactions

INTRODUCTION

Drug-drug interactions can occur when two or more drugs are administered simultaneously, and one of them increases or decreases the effectiveness of the other.[1] A clinician has to be aware of these drug interactions to avoid untoward events.

The consequences of drug interactions can vary from minimal to life threatening events. Infants, children, elderly, those with renal or hepatic impairment, and those who are on polypharmacy are at higher risk to develop adverse events due to drug interactions. The drugs that are more likely to produce adverse events (due to drug interactions) are those with a narrow therapeutic index or drugs that are recognized enzyme inhibitors or inducers.[2]

Drug interactions are broadly classified into pharmacokinetic and pharmacodynamic interactions.[3] Pharmacokinetic drug interactions refer to drug interactions that affect the processes by which drugs are absorbed, distributed, bound by plasma protein, sequestrated, metabolized, and excreted. When the effects of one drug are changed by the presence of another drug at the site of action, it is termed as pharmacodynamic interactions.[2]

With the current surge in recalcitrant dermatophytosis, many clinicians favor prolonged treatment with higher doses of systemic azole antifungals.[4] Azole antifungals show a wide range of interactions with many other medications, which are often overlooked.

Azole antifungals act as substrates as well as inhibitors of cytochrome P450 (CYP450) enzymes. They are also inhibitors of membrane transporters such as P glycoprotein. The inhibition or induction of CYP450 enzymes by azole antifungals may alter the pharmacokinetic profile of co-administered drugs that are metabolized through the same pathway. The risk of this pharmacokinetic interaction between an azole antifungal and another drug can differ, depending on the individual drug involved. The variations exist even for drugs within the same class.[5] Most

of the clinically relevant drug interactions associated with the azole antifungals are pharmacokinetic in nature (that affect either the gastrointestinal absorption or the metabolism).[3]

MECHANISM OF ACTION

Azole antifungals act by inhibiting the 14-α-demethylase enzyme. Azoles attain this by binding to the haem group of the enzyme which is required for conversion of lanosterol into ergosterol. Azoles thus exert their fungistatic activity by inducing deficiency of ergosterol in the fungal cell membrane and by causing accumulation of toxic precursors. The 14-α-demethylase belongs to the cytochrome P450 (CYP) family (CYP51A1). However, azoles also inhibit other isoenzymes of the CYP system leading to numerous drug interactions.[6]

This article deals with the pharmacokinetics and the clinically relevant and the common drug interactions involving two commonly used azole antifungals, fluconazole, and itraconazole.

PHARMACOKINETICS OF AZOLE ANTIFUNGALS

Fluconazole

Fluconazole is water soluble. It is absorbed rapidly and completely after oral administration with a bioavailability of >90%. Fluconazole has a low protein binding of 11–12%. The elimination half-life [$t_{1/2}$] of the drug is 30 hours and the absorption is unaffected by food or gastric acidity. Fluconazole circulates primarily as a free drug. It distributes readily into various body fluids (cerebrospinal fluid and urine) and tissues (liver, kidney, and central nervous system). Most of the drug (60–80%) is eliminated through the renal system where it undergoes glomerular filtration and tubular re-absorption.

Fluconazole has a variable, dose-dependent ability to inhibit CYP3A4 (especially with high daily doses), CYP2C9, and CYP2C19.[3,5-8]

Itraconazole

Itraconazole is a highly lipophilic drug. Being a weak base (ionized only at a low pH), itraconazole requires gastric acidity for adequate absorption. It should be taken immediately after a full meal for optimal absorption. Achlorhydria retards its absorption. Acidic beverages such as cola may increase its absorption while proton-pump inhibitors, H2-antagonists, and other antacids may retard the same.[6,9,10]

Itraconazole is highly protein bound (99.8%) and penetrates extensively into human tissues and has a $t_{1/2}$ of approximately 30 hours. It is metabolized by the liver (predominantly by the CYP3A4 isoenzyme system) and undergoes enterohepatic recirculation. Hydroxy- itraconazole is the major metabolite which shows an antifungal activity equal to that of the parent compound. Metabolites of itraconazole are excreted in urine and bile.[3,5,6]

DRUG INTERACTIONS

Interaction with statins

Among the statins, atorvastatin, lovastatin, and simvastatin are substrates for CYP3A4. Fluvastatin is a substrate for CYP2C9. Pravastatin and rosuvastatin are excreted primarily in the urine as unchanged drugs.[7]

Fluconazole, a potent inhibitor of CYP2C9 and CYP2C19, significantly alters the pharmacokinetics of fluvastatin.[7] Although fluconazole is a weak inhibitor of CYP3A4, there are reports that it can inhibit the metabolism of simvastatin and atorvastatin as well.[11,12]

As itraconazole is a potent CYP3A4 inhibitor, it significantly alters the pharmacokinetics of lovastatin, simvastatin, and atorvastatin (CYP3A-dependent statins).[7] The interactions between itraconazole or fluconazole and the statins can produce significant toxicity like rhabdomyolysis. It is a rare, but potentially severe side effect of elevated concentrations of HMG-CoA (3-hydroxy-3methylglutaryl coenzyme A) reductase inhibitors.[11,12] Therefore, when using itraconazole or fluconazole in patients on HMG-CoA reductase inhibitors, caution should be exercised and switching to alternative statin (pravastatin or rosuvastatin that are not metabolized by CYP3A4) should be considered.[7]

Interaction with benzodiazepines

Fluconazole and itraconazole inhibit the metabolism of benzodiazepines (mediated by CYP3A4). The interaction between the azoles and benzodiazepines is long lasting, especially with itraconazole. The metabolites of itraconazole play a significant role in the persistence of this interaction.[13,14] Metabolism of midazolam, triazolam, and diazepam may be inhibited by azoles.[3,7] The interactions can increase the pharmacodynamic effects of the benzodiazepines causing deep and prolonged sedative effects, prolonged amnesia, and reduced psychomotor performance. Benzodiazepines that are unaffected by concomitant administration of an azole are temazepam, bromazepam, and estazolam.[7]

Interaction with warfarin

Warfarin is a racemic mixture with R and S-isomers. R-warfarin is mainly metabolized by CYP3A4. 85% of S-warfarin is metabolized by CYP2C9. S-isomer is a more

potent (more than 5 times) antagonist of Vitamin K, in comparison to R-isomer.[15]

Fluconazole will potentiate the anticoagulant effect of warfarin by inhibition of CYP2C9. The interaction between fluconazole and warfarin can occur even if the dose of fluconazole is reduced by 50%. Hence, this combination should be avoided, if possible, as it increases the risk of significant bleeding.[16] If this is not possible, then the international normalized ratio (INR) must be closely monitored and the dose of warfarin should be adjusted accordingly.[7] Mootha *et al*. had reported a case of intraocular hemorrhage following warfarin - fluconazole interaction in a patient with Candida endophthalmitis.[17]

Since itraconazole is a strong inhibitor of CYP3A4 and has only a limited action on CYP2C9, theoretically it has less effect on the anticoagulant action of warfarin. Despite this, there are reports of itraconazole enhancing the anticoagulant action of warfarin.[18,19] Patients on warfarin with a high INR are at a greater risk of bleeding, after the introduction of an azole antifungal and need careful monitoring.[15]

Interaction with calcineurin inhibitors

Conversion of cyclosporine to its metabolites by CYP450 enzymes in the liver and the intestine is the rate limiting step in the elimination of the drug.[20] A randomized double blind study in renal allograft recipients on cyclosporine showed a slow increase in cyclosporine concentration over a period of 2 weeks, after starting fluconazole at a dose of 200 mg/day.[21] Fluconazole interacts with cyclosporine and tacrolimus in a dose-dependent manner. Due to the nephrotoxic potential of calcineurin inhibitors, dose reduction, close monitoring of their plasma concentration, and monitoring of renal function are mandatory when patients on cyclosporine or tacrolimus are prescribed more than 200 mg/day of fluconazole.[22,23] Fluconazole, by inhibiting the P450 enzyme in gut mucosa, inhibits the metabolism of calcineurin inhibitors in gut.[24] Hence, this interaction depends on the route of administration of the calcineurin inhibitors and is reported to be less with intravenous administration.

Significant interaction occurs between itraconazole and cyclosporine or tacrolimus regardless of the route of administration and hence an adjustment of dose is advised.[25,26] A dose reduction (of calcineurin inhibitors) protocol of 50% of recommended dose on starting the azole, 70% on day 3 and 75% on day 14 may ensure minimal change in serum levels of tacrolimus.[27]

Interaction with corticosteroids

Addisonian crisis was reported in a liver transplant recipient, who was on prednisone and fluconazole, after withdrawal of the latter. It was proposed that a reversal of the fluconazole induced suppression of P450 enzymes might have led to an alteration in steroid metabolism.[28] A hospital based study showed interaction between fluconazole and prednisone, but concluded the interaction to be of little clinical significance at the commonly prescribed doses. However, it is prudent to closely monitor steroid treated patients for any adverse event while introducing or withdrawing fluconazole.[29]

Itraconazole increases the plasma concentration of oral and intravenous methylprednisolone by inhibiting CYP3A4 mediated metabolism and by inhibition of P-glycoprotein mediated elimination. These in turn decrease the morning plasma cortisol level.[30-32]

Simultaneous administration of itraconazole and intravenous dexamethasone is reported to reduce the systemic clearance of the latter, thus enhancing it's adrenal suppressant effect.[33] Prednisolone shows only minor interaction with itraconazole which is of limited clinical significance. Hence, prednisolone should be the preferred steroid in combination with the azole antifungals.[32,34]

Metabolism of inhaled steroids such as budesonide and fluticasone is also inhibited by itraconazole resulting in suppression of morning plasma cortisol levels.[7]

Interaction with phenytoin

Azoles can interact with phenytoin in a bidirectional manner - azole first inhibits the CYP mediated metabolism of phenytoin, which is followed by the phenytoin induced CYP mediated metabolism of azoles.[7] There are case reports of fluconazole induced symptomatic phenytoin toxicity in patients on high doses (400 mg/day) of the former.[35,36] Data from a placebo controlled randomized study on healthy volunteers showed a significant increase in phenytoin concentration after simultaneous administration of fluconazole (200 mg/day for 14 days).[37] Patients receiving phenytoin or carbamazepine have shown treatment failure or relapse of fungal infections, when treated with azoles due to the phenytoin/carbamazepine induced metabolism of azoles.[3,38]

Interactions that decrease the systemic absorption of azoles

The azoles are weak bases and at higher pH, they dissolve more slowly.[7] H2-receptor antagonists, proton pump inhibitors and antacids reduce the absorption of itraconazole.[9,39,40] Absorption of fluconazole is unaffected by gastric pH.[7]

Co-administration of drugs such as phenytoin, phenobarbital, carbamazepine, rifampicin, isoniazid, ritonavir, efavirenz, and other inducers of CYP3A4 can induce the metabolism of azole antifungals. This in turn can result in failure of antifungal treatment.[3,7]

Table 1: Less commonly encountered drug interactions of azole antifungals.

Interacting drug	Mechanism	Effect
Astemizole	CYP3A4 substrate	Prolongs QT interval
Terfenadine	CYP3A4 substrate	Prolongs QT interval
Digoxin	Inhibition of P-gP protein	Increases digoxin levels
Nifedipine	CYP3A4 substrate	Increases nifedipine levels and peripheral edema
Glipizide	CYP2C9 substrate	Risk of hypoglycemia
Tolbutamide	CYP2C9 substrate	Risk of hypoglycemia
Tamoxifen	CYP3A4 substrate	Increases Tamoxifen levels
Vinca alkaloids	CYP3A4 substrate	Increases vinca alkaloid levels
Cyclophosphamide	CYP3A4 substrate	Increases cyclophosphamide levels
Busulfan	CYP3A4 substrate	Increases busulfan levels
Loperamide	CYP3A4 substrate, inhibition of P-gP	Increases loperamide levels
Sildenafil	CYP3A4 substrate	Increases sildenafil levels
Ritonavir	CYP3A4 substrate and CYP3A4 inhibitor	Increases levels of both azoles and ritonavir

P- gP: P glycoprotein

Table 1 shows the less commonly encountered drug interactions of azoles.

CONCLUSION

For the safe and effective use of azole antifungals, clinicians must be aware of their potential interactions with other drugs. An awareness regarding the possible consequences of drug interactions involving these commonly used drugs (azoles) may help the clinician to choose the most appropriate regimen for a particular patient and to ensure close monitoring to detect any adverse event as and when it occurs.

Declaration of patient consent

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Conflicts of interest

There are no conflicts of interest.

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