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REVIEW

Clinical safety and tolerability issues in use of triazole derivatives in management of fungal infections

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Abstract: There has been an increase in the number of patients susceptible to invasive fungal infections (IFIs) leading to a greater need for effective, well tolerated, and easily administered antifungal agents. The advent of triazoles has revolutionized the care of patients requiring treatment or prophylaxis for IFIs. However, triazoles have been associated with a number of adverse events and significant drug–drug interactions. While commonly used, physicians and patients should be aware of the distinct properties of these agents in order to ensure that patients are optimally treated with the least amount of toxicity possible. Clinicians should have a full understanding of the basic pharmacokinetics, absorption, and bioavailability of triazoles. Moreover, knowledge of the drug–drug interactions and potential toxicities of each agent is critical prior to administering a triazole. Careful history taking, thorough review of the patient's medication list, and detailed discussion with the patients and their families about the efficacy, safety, and tolerability of these agents should be performed. Clinicians treating patients with triazoles should closely follow them, monitor pertinent laboratory tests, and consider measuring drug levels as needed. This article will review the basic pharmacokinetic properties and most frequently encountered adverse events and pitfalls associated with triazoles in clinical practice.

Keywords: triazoles, fluconazole, voriconazole, posaconazole, itraconazole, review, invasive fungal infections, adverse events, drug–drug interactions

Introduction

The increasing number of patients susceptible to invasive fungal infections (IFIs), including patients with hematologic malignancies and hematopoietic stem cell transplant (HSCT) recipients, has led to a greater need for effective, well tolerated, and easily administered antifungal agents.[1–6] The advent of fluconazole in the early 1990s revolutionized the treatment of IFIs caused by *Candida* species (eg, esophageal candidiasis, candidemia).[7–9] The relatively narrow spectrum of fluconazole activity and increasing frequency of invasive mold infections (IMIs) resulted in the development of the mold-active azoles, ie, itraconazole, voriconazole, and more recently, posaconazole. Azoles share certain properties that make them desirable options for patients who are being treated for IFIs. All are available as oral formulations, are usually well tolerated, and most of them can be administered once or twice daily. Although when compared with amphotericin B products, there is a lack of any serious nephrotoxicity or infusion-related reactions, triazoles have been associated with a number of adverse events and significant drug–drug interactions. Therefore, it is important to understand the metabolism and side effects of triazoles, to review any patient's clinical history and medication list meticulously, and to monitor closely all patients treated with triazoles,

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in order to ensure successful and safe outcomes. This review will focus on the safety and tolerability of the four triazoles most frequently used in clinical practice (fluconazole, itraconazole, voriconazole, and posaconazole) and those aspects of these antifungals that are associated with direct patient care. The microbiologic spectrum and major therapeutic indications of the triazoles is beyond the scope of this article and will not be discussed here.

Clinical pharmacology of triazole agents

Triazoles are synthetic compounds with a chemical structure comprising one or more five-membered azole rings that contain three nitrogen atoms. They have a higher affinity for fungal than mammalian target enzymes, which makes them less toxic, for instance, than imidazole compounds like ketoconazole and miconazole. The currently available systemic triazoles are fluconazole, itraconazole, voriconazole, and posaconazole. Ravuconazole, albaconazole, and isavuconazole are in advanced stages of clinical development and will not be discussed in this article. In selecting the optimal triazole agent for therapy, it is important to consider not only its spectrum of activity, but also several other pharmacokinetic and pharmacodynamic parameters. There are limited data on pharmacodynamic properties of antifungal agents, but animal models suggest that killing of fungi with triazoles is optimized with maximal drug exposure over time (time-dependent killing).[10–12] The pharmacokinetic properties of triazoles, which include absorption, distribution, metabolism, and excretion, will be reviewed herein and are summarized in Table 1.

Fluconazole

Fluconazole was the first triazole available on the market and was approved by the Food and Drug Administration (FDA) in 1990. It is available in both intravenous (IV) and oral (PO) formulations (tablets and suspension) and has similar pharmacokinetic properties when administered by both routes. Following oral administration, fluconazole is very well absorbed with an absolute bioavailability of >90% when measured in normal volunteers.[13] Absorption of orally administered fluconazole is not affected by food or gastric pH.[14] Peak plasma concentration occurs one to two hours after oral administration and a steady state is reached within five to 10 days.[13] A loading dose (achieved by doubling the dose on the first day), can result in an increase in plasma concentrations nearing steady state within two days.[13] Fluconazole has a volume of distribution that approximates that of total body water and also

Table 1 Summary of major pharmacokinetic characteristics of oral triazole formulations

Agent	Bioavailability	Dosing	Dose adjustment for organ dysfunction	Protein-binding	Metabolism	Elimination half-life	CYP	Excretion	Active metabolite	CSF	Vitreous body
FLU	>90%	Load: 800 mg once IV/PO Maintenance: 100–800 mg/d IV/PO	Renal	12%	Minimal	20–50 hours	2C9, 3A4, 2C19	80% urine	–	>80%	20%–70%
ITR[1]	55%[2]	Load: 200 mg q8 h × 3 d Maintenance: 200 mg q12 h	None	99%	Liver	21–60 hours	3A4	<1% urine	Hydroxyl-ITR	<1%	~10%
VOR[1]	>95%	Load: 6 mg/kg q12 h IV/PO × 1 day Maintenance: 4 mg/kg IV/PO or 200–300 mg PO q12 h	Liver	58%	Liver	6 hours	2C19, 2C9, 3A4	<2% urine	–	~50%	38%
POS	NR	Load: 200 mg q6 h × 7 d Maintenance: 400 mg q8 h–12 h	None	98%	Liver[3]	35 hours	3A4	71% feces, 13% urine	–	variable	ND

Note: [1]Doses can be further adjusted based on drug levels or drug interactions; [2]oral solution; [3]uridine diphosphate glucuronidation.
Abbreviations: FLU, fluconazole; ITR, itraconazole; VOR, voriconazole; POS, posaconazole; CYP, cytochrome P450; CSF, cerebrospinal fluid; IV, intravenous; PO, oral; ND, no data; NR, not reported; d, day; h, hour.

has very low protein-binding which allows more free drug to be available. It has excellent tissue and body fluid penetration and achieves good concentration in the cerebrospinal fluid (CSF) and the vitreous humor. Hepatic metabolism plays a minimal role in the elimination of fluconazole, which is primarily cleared via the kidneys, with approximately 80% of the drug appearing unchanged in the urine.[13]

Itraconazole

Itraconazole is currently only available in capsule form and as a cyclodextrin itraconazole oral suspension, because the IV formulation has been withdrawn from the US market. The absorption of itraconazole is significantly impacted by the gastric pH, and peak plasma concentrations can be reached within one to four hours and a steady state within seven to 14 days in normal, healthy volunteers. Itraconazole has a high volume of distribution, is highly lipophilic, and has very good distribution in various tissues including lung, liver, esophagus, and stomach. Itraconazole is primarily metabolized via the cytochrome P450 (CYP450) system's 3A4 isoenzyme, and its major active metabolite is hydroxyl-itraconazole.[15] Itraconazole and its active metabolite are heavily protein bound (>95%), hence their penetration into the CSF is minimal (<1%). One pharmacokinetic study suggests that itraconazole may undergo saturable metabolism with multiple dosing.[16]

Voriconazole

Voriconazole is available as both an IV (solubilized in cyclodextrin) and oral formulations (tablets and suspension). It is 58% protein-bound, with a large volume of distribution of approximately 4.6 L/kg, suggesting extensive distribution into the tissues. Voriconazole penetrates well into the CSF, vitreous, and aqueous, with respective concentrations in these compartments of 50%, 38.1%, and 53% the concentration found in plasma.[17,18] Voriconazole is metabolized in the liver, predominately via the CYP2C19 isoenzyme and to a smaller degree by CYP2C9 and CYP3A4. Its major metabolite, N-oxide, does not appear to have any significant antifungal activity.[19] Notably, voriconazole exhibits nonlinear pharmacokinetics due to saturation of its metabolism and therefore a proportional increase in plasma levels is not achieved by simply increasing the dose.[20] Administering a loading dose however, may allow approximate plasma concentrations closer to steady state within one day in comparison to five or six days without a loading dose.[19]

Posaconazole

Posaconazole is currently only available as a suspension for oral administration. Bioavailability is significantly increased when administered with food, especially with a high-fat meal and can be further enhanced by increasing the frequency of administration of the drug rather than the quantity of the administered dose.[21–24] Peak plasma concentrations are attained within three to five hours after each oral administration and steady-state plasma concentrations are achieved within seven to 10 days with a regular dosing schedule. Posaconazole has a large volume of distribution, suggesting extensive tissue distribution. Limited data suggest that posaconazole has variable CSF penetration, ranging from undetectable to 237%; no data are available on posaconazole penetration into the vitreous body.[25,26] It is primarily metabolized in the liver through glucuronidation to biologically inactive metabolites and is predominantly eliminated in the feces.

Therapeutic perspectives and practical implications

The triazoles are a class of antifungal medications with significant adverse events, drug–drug interactions, and potentially variable serum concentrations. Basic concepts and common pitfalls associated with dosing, administration, and absorption of triazoles will be reviewed in this section.

Dosing of triazoles

Selection of the optimum dose of triazoles can be challenging because of the variable pharmacokinetics, absorption, and drug–drug interactions that these antifungals exhibit. Available data suggest that more than one-third of patients with candidemia may receive inadequate therapeutic dosing of fluconazole.[27,28] Important considerations with triazole dosing include administration of a loading dose, dose adjustment in patients with renal or hepatic dysfunction, and dose adjustment in the presence of concomitant medications with potential drug–drug interactions. In order to attain more rapid therapeutic concentrations close to steady state, current guidelines recommend administering a loading dose of the triazole being used.[29,30] There are some data suggesting that clinicians occasionally neglect to use loading doses when prescribing a triazole.[27,28,31] The duration of administration of the loading doses varies according to the antifungal agent used. The duration for fluconazole and voriconazole is the first 24 hours, for itraconazole the first three days, and for posaconazole the first seven days.

Fluconazole is minimally metabolized and 80% of the drug is excreted unchanged in the urine and, for that reason, is the only azole that needs to be dose-adjusted in patients with impaired renal function.[13] In contrast, voriconazole is metabolized by the liver and there is no need for dose-adjustment in

patients with renal impairment, because only 2% of voriconazole is excreted in the urine. In patients with mild to moderate hepatic impairment, voriconazole should be dose-adjusted using the Child-Pugh scoring system.[19] Special note should be made to avoid the administration of IV voriconazole in patients with renal impairment (creatinine clearance <50 mL/min), because of the potential accumulation of cyclodextrin, the solubilizing vehicle contained in this formulation.[19]

Voriconazole and CYP polymorphisms

Voriconazole is metabolized primarily by the CYP2C19 enzyme. The CYP2C19 allele exhibits genetic polymorphism, resulting in three different phenotypes in patients, ie, homozygous-poor metabolizers, homozygous-extensive metabolizers, and heterozygous-intermediate metabolizers. Significant genetic variability in CYP2C19 has been reported and 15–20% of Asians and 2% of Caucasians have been found to be homozygous-poor enzyme metabolizers, which is associated with higher levels of voriconazole due to slower metabolism.[32–34] A number of patients have also been found to be heterozygous for the CYP2C19 allele, which can be associated with moderately higher voriconazole levels than expected.[34] Even though there are no current guidelines for routine testing of the CYP2C19 allele among patients treated with voriconazole in order to follow drug levels, clinicians should closely monitor their patients for potential voriconazole-associated toxicities, in particular, patients of Asian descent.

Weight considerations

Limited data exist on dosing of triazoles in obese patients (body mass index ≥30). Weight-based dosing, in mg/kg of fluconazole in obese patients should be used because there is an increase in clearance of fluconazole in this patient category, possibly as a result of the higher volume of distribution.[35] There are no data on pharmacokinetics and dosing of itraconazole, voriconazole, and posaconazole in obese patients.

Administration and absorption of triazoles

Ingestion or lack of food and other substances can significantly affect the absorption and efficacy of certain triazoles. Fluconazole is the only triazole whose absorption is not affected by food or by gastric pH. In contrast, itraconazole has varied absorption patterns depending on the formulation prescribed. Itraconazole suspension is better absorbed on an empty stomach and absorption may decrease by up to 40% if taken with nonfatty meals.[14,15,36,37] Itraconazole capsules require an acidic gastric pH and hence should be administered with food.[15,38] Coadministration with cola products or cranberry juice increases absorption and should be discussed with patients in an effort to enhance compliance and efficacy. Proton pump inhibitors, H_2 blockers, and antacids may compromise the absorption of itraconazole capsules due to gastric acidity reduction. In patients who require gastric protection, itraconazole capsule should not be prescribed and other options should be considered. The absorption of voriconazole may be reduced by 20%–30% when taken with food and, therefore, administration of voriconazole on an empty stomach or at least one hour before food is recommended. Data suggest that coadministration with omeprazole may increase the area under the curve of voriconazole by 40%.[39] Posaconazole is available only as an oral formulation and bioavailability depends on coadministration with meals and frequency of dosing.[22,23] Studies in healthy volunteers have shown that administration of posaconazole with food, and especially a high-fat meal, increase drug absorption.[40,41] Mean increases of up to 400% and 264% have been measured when given with a high-fat and low-fat meal, respectively, in comparison with the area under the curve of the drug when in the fasting state.[40,41] Gastric pH does not appear to affect the absorption of this agent, although some data suggest that coadministration with cimetidine or a proton pump inhibitor (eg, omeprazole) may be associated with decreased levels.[40,42–44]

Limited data exist regarding the absorption of triazoles in patients with impaired gastrointestinal mucosal integrity resulting from chemotherapy-induced mucositis or graft versus host disease (GVHD). This is pertinent for patients with hematologic malignancies and HSCT recipients, because the presence of mucositis or GVHD of the gastrointestinal tract may lead to variable absorption and inadequate plasma concentrations of the administered triazole. In a sub-analysis of a prospective randomized study comparing posaconazole at 200 mg orally three times daily with fluconazole for antifungal prophylaxis among allogeneic HSCT recipients with GVHD, patients with acute GVHD or/and diarrhea had lower plasma concentrations of posaconazole.[45,46] Posaconazole levels appeared to be lower in five patients who developed a breakthrough IFI compared with patients who did not develop an IFI.[45,46] The potential effect of gastrointestinal GVHD or mucositis, occasional difficulty of coadministration of posaconazole with meals, and active diarrhea or vomiting should prompt careful monitoring of these patients, including monitoring of drug levels in order to ensure adequate

coverage.[47] These data underscore the importance of close communication between the clinician and those patients treated with posaconazole.

Little is known about other routes of administration of the triazoles. Certain patient categories, for instance critically ill patients in the intensive care unit or patients with severe mucositis, may require administration of medications via a nasogastric tube (NGT). In addition, an increasing number of patients are discharged with an NGT or a percutaneous endoscopic gastrostomy (PEG) tube. At present, there is a paucity of data about the absorption of triazoles through an NGT or PEG tube to guide therapeutic decisions.[48–52] Coadministration of a single dose of 400 mg of posaconazole with a nutritional supplement via an NGT in healthy volunteers was associated with lower concentrations of the drug up to 20% compared with oral administration, in a Phase 1, open-label, single-center, randomized, crossover study.[52] Intersubject variability was observed and issues, such as posaconazole absorption in sick NGT-fed patients and concentrations following routine loading doses of posaconazole, were not addressed.[52] While more data are required, it appears that posaconazole suspension may be administered via an NGT with nutritional supplements and close plasma level monitoring for dose adjustment.

Other instances that may be associated with poor absorption of mold-active triazoles, especially of posaconazole, are when treating patients with cystic fibrosis because a lack of pancreatic enzymes can potentially decrease the absorption of the triazole. In an observational study of 35 lung transplant recipients with cystic fibrosis treated with voriconazole, plasma concentrations higher than 0.5 mg/L were attained in only 20% of the patients and administration of higher doses of voriconazole, IV administration of the drug, and/or concomitant use of other antifungal agents were required in a number of patients to attain the same efficacy.[53] Consultation with an infectious diseases specialist should be sought in order to ensure that therapeutic levels will be attained if administration of other antifungal agents is not possible and treatment with posaconazole cannot be avoided. Careful review of each case individually should be performed before definitive recommendations can be given.

Pregnancy

Limited data exist on the use of triazoles in pregnant women, however all triazoles have been found to be teratogenic in animal studies.[13,15,19,21] Moreover, prolonged administration of fluconazole in pregnant women has been associated with congenital abnormalities.[54,55] However, several studies suggest that short courses of fluconazole in pregnant women may not lead to a higher risk for congenital malformation.[54,56,57] Furthermore, animal models suggest that fluconazole-associated teratogenicity may be dose-related.[58] Data on itraconazole safety during pregnancy in humans is limited to two prospective European cohort studies which did not show increased risk for major congenital abnormalities.[59,60] However, rates of spontaneous and induced abortion were higher in women who received itraconazole in one study.[60] There are no human studies of voriconazole and posaconazole safety during pregnancy to the date. Fluconazole, itraconazole, and posaconazole are labelled as pregnancy category C medications and should not be used in pregnant women unless the benefit outweighs the risk, while voriconazole belongs to pregnancy category D medications and is contraindicated in pregnant women.[13,15,19,21] Due to the limited data on the effect of triazoles when nursing, their administration is not recommended for nursing mothers unless the benefit to the mother outweighs the potential risk to the infant.[13,15,19,21]

Drug–drug interactions

All triazoles exhibit some degree of drug–drug interactions due to their metabolism by the CYP450 system, as they can be substrates, inducers, and inhibitors of CYP enzymes, and coadministration with other agents that interfere with the CYP450 system may result in significant alteration of plasma triazole levels. P-glycoprotein is a transporter protein involved in the absorption and distribution of triazoles. Triazoles can function as substrates for P-glycoprotein and/or inhibitors, thus creating drug–drug interactions with other agents that also interact with this protein. It is crucial for clinicians to understand the mechanisms and potential drug–drug interactions with each triazole. Voriconazole and itraconazole appear to be more potent inhibitors of CYP450 compared with fluconazole and posaconazole.[61] Fluconazole is a substrate of CYP3A4 and inhibitor of CYP2C9 and 2C19, and its interactions with other agents often appear to be dose-dependent. Itraconazole and its major metabolite, hydroxyl-itraconazole, are substrates and inhibitors of CYP3A4. Additionally, itraconazole is a substrate and inhibitor of the P-glycoprotein. Voriconazole is both a substrate and inhibitor of CYP2C19, CYP2C9, and CYP3A4, with highest affinity for CYP2C19, followed by CYP2C9. Its major metabolite N-oxide inhibits CYP3A4 and CYP2C9 to a greater extent than CPY2C19. Posaconazole is metabolized via the uridine diphosphate glucuronidation pathway; it is a substrate and inhibitor of the P-glycoprotein and a CYP3A4 inhibitor. There are a

significant number of clinically important drug interactions that occur with all triazoles and careful consideration should be given when these agents are added to or discontinued from a patient's drug regimen because adjustment of doses of the remaining medications may be necessary. Complete review of CYP450 mediated drug interactions with triazoles is beyond the scope of this article and key interactions are summarized in Table 2.

Major adverse events: Patient tolerability and compliance

The following section will discuss the major adverse events and impact of triazoles on patients' activities of daily living and quality of life. Hepatotoxicity will be reviewed as an overall adverse event, rather than individually with each agent, as all triazoles may have an effect on liver function. Special consideration will be given to voriconazole because of its more complicated adverse event profile.

Hepatotoxicity

All triazoles have been associated with some degree of hepatotoxicity, ranging from mild hepatitis to cholestasis and, rarely, fulminant hepatic failure.[13,15,19,21] Although not entirely clear, it appears that liver toxicity may be related to higher plasma drug levels, with most data coming from patients treated with voriconazole (abnormal liver tests between 2.9% and 33.3%, Table 3). There are no definitive guidelines to help clinicians decide when and how often to check liver tests and when it is appropriate to discontinue treatment due to hepatic impairment. Physicians should monitor liver function tests in patients taking triazoles during the first couple of weeks of treatment. Further decisions in case of abnormal results should be made based on critical assessment of each case individually and in consultation with an infectious diseases specialist. Because liver toxicity can have many potential causes in a subset of patients requiring treatment with a triazole, including comorbid conditions and treatment with other potentially hepatotoxic medications, clinicians should concomitantly investigate other causes of hepatic impairment.

Fluconazole

In addition to potential hetatotoxicity, patients treated with fluconazole may develop alopecia. In a review of patients treated with fluconazole alopecia was reported in up to 12.5% to 20% of cases; the vast majority of patients received 400 mg of fluconazole for a mean of 7.1 months.[62] Alopecia most commonly occurs after prolonged treatment courses (median of three months in one study) and it may be subtle, starting indolently, and even go unnoticed initially.[62] Extensive hair loss requiring use of a wig has been reported in a small number of patients.[62] In one review, alopecia was reversible within six months upon discontinuation of therapy with fluconazole or reduction of the dose by at least 50%.[62] Patients on prolonged treatment courses with fluconazole should be counselled accordingly and asked about hair loss during followup visits.

Itraconazole

Gastrointestinal symptoms, including nausea, vomiting, and diarrhea, are the most prominent and commonly reported side effects observed in patients treated with itraconazole. This is more common when itraconazole oral solution is used, predominantly as a result of the cyclodextrin vehicle used in this formulation. Although itraconazole solution is better absorbed than the capsule, gastrointestinal toxicity may significantly decrease patient compliance, and changing to the capsule form may be necessary. Two rare, but significant, side effects of itraconazole must also be discussed. Congestive heart failure, likely due to a direct negative inotropic effect of the drug, has led to a "black box" warning for itraconazole and treating physicians should thoroughly review their patients' medical conditions and medication list prior to prescribing this agent.[63] An aldosterone-like effect leading to hypokalemia, hypertension, and occasionally peripheral edema has also been associated with itraconazole use, so careful electrolyte monitoring is warranted.[64]

Voriconazole

Visual changes

Visual changes in patients treated with voriconazole range from 4.0% to 44.8% (Table 3).[65–71] Symptoms vary and include enhanced light perception, blurred vision, wavy or zigzag lines, increased "brightness" perception, altered visual or color perception, or photophobia.[71,72] These are transient effects that occur shortly after administration of the drug, primarily observed with the first infusion, and tend to fade with subsequent infusions.[68,71] In the vast majority of patients these visual changes do not require any interventions or discontinuation of the administered drug.[67,68,71] However, dose adjustment may be required because recent data suggest an association between voriconazole levels and visual adverse events.[73] Patients and their families should be made aware of the various "visual effects" of voriconazole and patients cautioned about their ability to drive, particularly

Table 2 Summary of major documented and potential drug–drug interactions of triazoles*

Type of interaction and agent involved	Triazole	Recommendation
Decrease triazole plasma concentrations		
Rifampin	VOR, ITR, FLU, POS	Contraindicated with VOR, monitor ITR levels, consider increasing FLU dose
High dose ritonavir (400 mg BID), St John's wort	VOR	Contraindicated
Carbamazepine, long-acting barbiturates (eg, phenobarbital)	VOR, ITR	Contraindicated with VOR, monitor ADE and levels with ITR
Low-dose ritonavir (100 mg BID)	VOR	Avoid combination
Cimetidine, efavirenz	POS	Avoid combination
Esomeprazole, metoclopramide	POS	Monitor POS levels and breakthrough infections
Phenytoin, nevirapine	ITR	Monitor ITR levels and breakthrough infections
Plasma concentrations increased by triazole		
Levacetylmethadol	ITR	Contraindicated
Astemizole, terfenadine	VOR, FLU	Contraindicated with VOR, FLU $\geq$ 400 mg is contraindicated with terfenadine, monitor ADE
Cisapride	VOR, POS, ITR FLU	Contraindicated
Pimozide, ergot alkaloids (eg, ergotamine)	VOR, POS, ITR	Contraindicated
Quinidine, dofetilide	VOR, POS, ITR	Quinidine contraindicated, dofetilide contraindicated only with ITR
Sirolimus	VOR, POS, ITR	Contraindicated with VOR, POS; monitor levels and ADE with ITR
Tacrolimus, cyclosporine	VOR, POS, ITR, FLU	Reduce dose, monitor levels
Methadone, short-acting opioids (eg, sufentanil),	VOR	Monitor ADE, dose reduction may be needed
Warfarin	VOR, ITR, FLU	Monitor PT, INR levels
Digoxin	ITR	Monitor ADE
Theophylline	FLU	Monitor theophylline levels
Plasma concentrations potentially increased by triazole		
Benzodiazepines	VOR, ITR, FLU	Triazolam, oral midazolam are contraindicated with ITR; monitor ADE, consider dose reduction
Statins	VOR, ITR	Lovastatin, simvastatin are contraindicated with ITR; monitor ADE, consider dose reduction
Calcium channel blockers	VOR, POS, ITR	Nisoldipine is contraindicated with ITR, monitor ADE with other agents
Oral hypoglycemic, vinca alkaloids	VOR, POS, ITR, FLU	Monitor ADE
Other NNRTIs, other protease inhibitors	VOR, POS, ITR	Monitor ADE
Disopyramide	ITR	Monitor QT_c interval, other ADE
Two-way interactions		
Rifabutin	VOR, POS, ITR	Contraindicated with VOR, avoid combination with POS, ITR
Efavirenz	VOR	Increase VOR dose, reduce efavirenz dose
Phenytoin	VOR, POS	Increase VOR dose, monitor phenytoin levels and ADE
Omeprazole	VOR	Reduce omeprazole dose to ½ if >40 mg/day
Oral contraceptives	VOR	Monitor for ADE of both agents and voriconazole levels

Notes: *Table adjusted based on.[13,15,19,21]

Abbreviations: BID, twice daily; FLU, fluconazole; ITR, itraconazole; VOR, voriconazole; POS, posaconazole; ADE, adverse events; PT, prothrombin time; INR, International Normalized Ratio.

Table 3 Review of major studies reporting on adverse events associated with voriconazole

Study	n	Patient population	Indication	Nausea	Chills	Fever	Visual hallucinations	Visual changes	Liver enzymes	Rash
65	200	Immunocompromised hosts	Esophageal candidiasis	6%	NR	12%	NR	23%	6.5%[1]	5.5%
68	415	Heme malignancy, solid tumor, HSCT	Neutropenic fever	9.4%	13.7%	NR	4.3%	21.9%	2.9%–8.9%[2]	3.4%[3]
70	194	Heme malignancy, HSCT/SOT	IA	NR	3.1%[4]	3.1%[4]	6.7%	44.8%	3.6%	8.2%
71	137	Heme malignancy, HSCT/SOT, DM, HIV	IA	2.2%	NR	NR	NR	10.9%	14.6%[5]	8.8%
96	45	Heme malignancy, HSCT/SOT	IMI	2.2%	NR	NR	NR	NR	8.9%	2.2%
66	52	Heme malignancy, SOT, HIV, other[6]	IC	25%	NR	NR	NR	21.2%	23%[7]	15.4%
69	272	NR	IC	NR	3%	15%	NR	4%	23%	6%
67	39	Heme malignancy, HSCT/SOT, other	IA, CPA	NR	NR	NR	NR	30.8%[8]	33.3%	35.9%[9]

Notes: [1]Elevation of alkaline phosphatase only reported; [2]Including together elevation of transaminases and alkaline phosphatase $>5 \times$ the baseline value; [3]flushing; [4]rates for chills and fevers reported together; [5]3–5 $\times$ upper normal limit; [6]other, chronic obstructive pulmonary disease, tuberculosis, bronchiectasis, diabetes mellitus, alcoholism; [7]predominantly elevated transaminases; [8]visual changes defined as: enhanced light perception, photophobia, color vision changes, blurred vision, and wavy lines on television or on going to sleep; [9]rash in 6 patients, photosensitivity in 3 patients, and cheilitis in 5 patients.

Abbreviations: n, number of patients; NR, not reported; heme, hematologic; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant; IA, invasive aspergillosis; DM, diabetes mellitus; IMI, invasive mold infection; IC, invasive candidiasis; CPA, chronic pulmonary aspergillosis.

in the dark. Professional drivers, patients that drive to work, those that use computers or screens, and/or work during the night should be further educated and advised to seek medical attention as needed.

Central nervous system toxicity

Although poorly described, rates of visual hallucinations range from 4.3 to 6.7%.[74] Interestingly, the majority of patients seem to be aware of these symptoms, frequently finding them pleasant.[74] Amongst others, descriptions of these visual hallucinations have included "objects crawling on the wall" and "people being in the room".[74] Other CNS symptoms, including auditory hallucinations, confusion, hypotonia, irritability, and agitation have been reported in patients taking voriconazole.[74,75] These symptoms appear to be dose-related and tend to present after one week of treatment (range 3–30 days in one study).[39,75] Neurotoxicity has been associated with increased levels of voriconazole (plasma troughs >5.5 mg/L).[39,75] Given that a number of patients requiring treatment with voriconazole may also be on psychotropic drugs or at risk for CNS infections that may present with hallucinations or confusion, making the diagnostic distinction can be difficult. Such symptoms should always be investigated and while voriconazole toxicity should be included in the differential diagnosis, all efforts should be made to rule out any other potential causes of these symptoms (eg, infectious meningo-encephalitis, other drug toxicities, etc.).

Skin reactions

A brief review of the major voriconazole clinical trials reveals an incidence of skin rash among patients receiving voriconazole ranging from 2.2% to 35.9%.[68–71,76,77] Skin reactions can present as a facial erythema, pruritus, hyperpigmentation, pseudoporphyria, or cheilitis.[71,72,78–83] Reactions can be mild to severe, but discontinuation of voriconazole due to a severe skin reaction has rarely been reported.[71] An increasing number of patients receive voriconazole for extended periods of time whilst performing daily activities in their communities, hence photosensitivity reactions may increase. Moreover, there have been reports of cases of skin cancer with sun exposure in patients taking voriconazole.[84] Because use of sunscreen appears to have some protective effect, clinicians should make appropriate recommendations to their patients and be vigilant about this infrequent adverse event.[85] It is advised that patients, particularly children, who spend a significant part of their day outside, should be made aware of this side effect, wear sunscreen, and use long-sleeved shirts if possible. In cases of severe photosensitivity reactions, other agents should be considered, and close monitoring and followup of these patients reinforced.

Table 4 Review of major studies reporting on adverse events associated with posaconazole

Study	n	Patient population	Dose	Nausea	Vomiting	Headache	Dizziness	QT prolongation	Rash	Liver enzymes	AST	ALT	ALP
97	448	Healthy volunteers	50–1200 mg/d	NR	NR	17%	6%	None	NR	NR	6%	11%	NR
87	330	Cancer, HSCT	800 mg/d	14%	6%	5%	5%	5%	NR	NR	5%	NR	5%
86	23	SOT	800 mg/d	17.4%	8.7%	NR	NR	NR	NR	NR	8.7%	4.3%	NR
98	53	Heme, HSCT	800 mg/d	NR	NR	NR	NR	NR	NR	NR	0	NR	0
88	107	Cancer, HSCT/SOT, other[1]	800 mg/d	12%	5%	<3%	<3%	0	4%	3%	NR	2%	NR
99	304	AML/MDS	600 mg/d	NR	NR	NR	NR	<1%	NR	<1%	NR	<1%	NR
45	301	HSCT	600 mg/d	7%	4%	1%	NR	NR	NR	3%	3%	3%	NR
100	428	Cancer, HSCT/SOT, other[2]	800–1200 mg/d	8%	7%	9%	2%	2%	3%	2%	3%	5%	NR
101	21	Cancer, HSCT/SOT, DM	800 mg/d	5%	5%	NR	NR	0	5%	NR	5%	NR	NR

Notes: [1]Other, diabetes mellitus, HIV/AIDS; [2]Other, acquired immunocompromising conditions, no known underlying immunocompromising conditions.
Abbreviations: n, number of patients; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; d, day; NR, not reported; heme, hematologic malignancy; HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; DM, diabetes mellitus.

Posaconazole

The most commonly reported side effects related to posaconazole include nausea (5%–17.4%) and vomiting (4%–8.7%) (Table 4).[45,86–88] Because erratic absorption of this agent is one of its major limitations, patients should be carefully monitored and routinely interviewed about possible gastrointestinal complaints that could further compromise the absorption and efficacy of the drug. A potentially significant, albeit rare (1%–5%) side effect is QT_c prolongation and torsades de pointes (Table 4). Careful review of the patient's medication list should be performed and posaconazole should be avoided in the presence of concomitantly administered agents with potential effect on the QT_c interval.

Therapeutic drug level monitoring

With the exception of itraconazole, there are no definitive recommendations for therapeutic drug monitoring for other triazoles.[89] Fluconazole, due to its linear pharmacokinetics and its long clinical experience, does not require therapeutic drug monitoring. In the case of itraconazole, therapeutic drug monitoring is suggested one to two weeks after treatment initiation to ensure therapeutic levels.[89,90] Using high-performance liquid chromatography (HPLC), plasma levels for itraconazole and hydroxyl-itraconazole can be accurately measured. Although the therapeutic itraconazole concentration range has not been defined as yet, a random itraconazole level of at least 1.0 μg/mL is recommended for the treatment of histoplasmosis.[90] Posaconazole has a long half-life and although it may take up to 100 hours to reach a steady state, adequate therapeutic levels may be attained within one to two days.[91] Posaconazole peak and average concentrations of 1.50 mg/L and 1.25 mg/L, respectively, have been associated with 75% response rates.[88] However, very limited data on posaconazole levels are available to date, and these do not allow for any meaningful conclusions. Expert recommendations include measuring posaconazole levels in patients with mucositis, gastrointestinal GVHD, and those with concerns of decreased absorption.[46,47]

Multiple reports have underscored the variability of voriconazole plasma levels.[39,92–94] In a review of HSCT recipients receiving standard voriconazole doses, plasma trough voriconazole levels were undetectable in 15% of patients.[95] Limited data from uncontrolled studies, most of them retrospective, in different patient populations, and measuring random or trough plasma voriconazole levels show that trough levels of voriconazole >1 μg/mL may be associated with improved outcomes.[39,73,75,93–95] Higher voriconazole levels have been associated with visual adverse events, neurologic toxicities, and elevated aspartate aminotransferase and alkaline phosphatase.[39,73,75] Despite the possible limitations of

these studies, suggested target plasma voriconazole trough levels are between 1.0 and 5.5 μg/mL.[39] More prospective data are required to make definitive recommendations, and clinicians should consider obtaining plasma voriconazole levels in patients who appear not to respond to treatment, those with significant drug–drug interactions, and with evidence of voriconazole-associated toxicities.

Conclusions

The advent of triazoles has revolutionized the care of patients requiring treatment or prophylaxis for IFIs. While commonly used, physicians and patients should be aware of the distinct properties of these agents in order to ensure that patients are optimally treated with the least amount of toxicity possible. Favorable outcomes require critical assessment and selection of the appropriate therapeutic agent for each patient. This decision should be based on the type of infection treated, the patient category, and the efficacy and toxicities of the selected agent. Drug–drug interactions and the various side effects of triazoles can significantly impact patients' lifestyle. Clinicians should have a full understanding of the basic pharmacokinetics, absorption, and bioavailability of these drugs. Moreover, knowledge of the drug–drug interactions and potential toxicities of each agent is critical prior to administering a triazole. Careful history taking, thorough review of the patient's medication list, and detailed discussion with the patients and their families about the efficacy, safety, and tolerability of these agents should be performed. Clinicians treating patients with triazoles should closely follow them, monitor pertinent laboratory tests, and consider measuring drug levels as needed. Consultation with an infectious diseases expert should be sought if feasible.

Disclosures

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