Received: 27 March 2023 | Revised: 23 May 2023 | Accepted: 26 May 2023

DOI: 10.1002/phar.2850

PHARMACOTHERAPY accp

REVIEW OF THERAPEUTICS

INSIGHTS FROM SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Utility of triazole antifungal therapeutic drug monitoring: Insights from the Society of Infectious Diseases Pharmacists

Endorsed by the Mycoses Study Group Education and Research Consortium

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Abstract

Triazole antifungals (i.e., fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole) are commonly used in clinical practice to prevent or treat invasive fungal infections. Most triazole antifungals require therapeutic drug monitoring (TDM) due to highly variable pharmacokinetics, known drug interactions, and established relationships between exposure and response. On behalf of the Society of Infectious Diseases Pharmacists (SIDP), this insight describes the pharmacokinetic principles and pharmacodynamic targets of commonly used triazole antifungals and provides the rationale for utility of TDM within each agent.

KEYWORDS
fluconazole, isavuconazole, itraconazole, pharmacodynamics, pharmacokinetics, posaconazole, voriconazole

1 | EXECUTIVE SUMMARY

Fungal infections cause significant morbidity and mortality globally, with over 13 million infections and 1.5 million deaths each year.[1] In 2018, more than 600,000 fungal infections were diagnosed in hospitalized patients in the United States with estimated costs of over $6.7 billion.[2] During the COVID-19 pandemic, the incidence of life-threatening fungal infections such as mucormycosis, aspergillosis,

and invasive candidiasis including *C. auris* surged. The challenges in managing invasive fungal infections (IFIs) in these complex patients have further heightened awareness of the need to optimize antifungal use. Although there are several new antifungal agents in the pipeline, triazoles continue to be the mainstay of therapy for the treatment and prevention of IFIs, but their clinical use is complicated by variable pharmacokinetics and drug–drug interactions. Therefore, there is increased recognition of the need for antifungal stewardship and practical guidance for therapeutic drug monitoring (TDM) for patients with IFIs. The Infectious Diseases Society of America (IDSA) and other international organizations have recommended TDM for mold-active triazoles when used for the prevention or treatment of IFIs such as aspergillosis. Despite these recommendations, TDM was performed only in approximately half of patients receiving voriconazole or posaconazole for prevention or treatment of IFI in a recent large multi-center study.[3]

The recent publication of additional TDM recommendations from several different groups offers the opportunity to highlight areas of consensus and identify where controversies and unanswered questions remain (Table 1). An international interdisciplinary expert panel of members with research and/or clinical experience in antifungal pharmacotherapy was convened to review the literature and formulate insights for best practice for triazole antifungal TDM. Herein, the Society of Infectious Diseases Pharmacists (SIDP) offers these insights on the updated literature regarding triazole antifungal TDM and summarizes evidence (Appendix S1) supporting the utility of TDM for azoles in the prevention and management of IFIs.

TDM remains the most straightforward approach for determining whether suspected breakthrough infection or observed toxicities are developing in the setting of low or excessive systemic drug exposures, respectively. Preemptive identification of subtherapeutic or potentially toxic drug exposures may also guide dosing adjustments that reduce the risk of poor outcomes. Given the challenges associated with early diagnosis of breakthrough fungal disease and the high mortality and impact such infections have on treatment of underlying diseases, TDM remains a useful tool for assessing triazole exposures in conjunction with other clinical, laboratory and radiological criteria.

2 | THERAPEUTIC DRUG MONITORING BEST PRACTICES

Drawing from the literature, review of current published guidelines, and the authors' collective clinical experience, we have identified three triazoles where TDM should be routinely employed: voriconazole, posaconazole, and itraconazole. TDM for fluconazole and isavuconazole may be recommended in specific circumstances, as outlined below. For pediatric patients, there may be additional considerations for timing of levels and dosing due to altered pharmacokinetics, but the general concepts for TDM goals are also applicable in this population. Timing, target concentrations, and special considerations for TDM for each azole are summarized in Table 1.

2.1 | Voriconazole

Given the marked intra- and inter-patient pharmacokinetic variability with voriconazole dosing and the association of its plasma concentrations with both efficacy and toxicity, voriconazole concentrations should be routinely monitored in patients receiving this agent for prophylaxis or treatment.[4,5] Trough concentrations drawn typically 5 days (or as early as day 2 if a loading dose is administered) after initiation, dose adjustment, or with the initiation or cessation of an interacting medication should be obtained and potentially repeated during a course of therapy to document continued therapeutic concentrations. A trough goal of 1–5.5 mg/L is reasonable for most infections, although a narrower range of 1–4 mg/L has also been recommended to avoid toxicities. Some experts recommend a trough concentration >2 mg/L for the treatment of invasive aspergillosis.[6]

Voriconazole trough concentrations of >5–5.5 mg/L are associated with an approximate fourfold increased risk of toxicity.[7–9] In a randomized trial of 108 evaluable patients (with predominantly *Aspergillus* spp. infections), TDM of voriconazole was associated with a reduction in discontinuation of therapy due to adverse events and higher complete/partial response to therapy.[4]

More sophisticated pharmacometric models recently developed may optimize voriconazole dosing based on pharmacodynamic parameters.[10,11] Dosing algorithms and specialized software have also been developed to aid the adjustment of voriconazole dosing to achieve target concentrations more readily.[12] Practically, dose adjustments are made in increments of 50–100 mg due to tablet size; TDM must be performed after dose adjustment since metabolism is nonlinear. TDM should also be performed after converting from intravenous to oral formulation (or vice versa) due to variations in absorption and metabolism. Metabolizer phenotypes, hypermetabolic states, and interacting drugs must be carefully taken into consideration when designing or adjusting a dosage regimen for voriconazole. For subtherapeutic concentrations, it may be necessary to dose more frequently than every 12 h, add cytochrome P450 (CYP450) inhibitors such as omeprazole to the regimen, or discontinue CYP450 inducers.[13] Although obtaining a CYP2C19 genotype is not currently the standard-of-care for most patients receiving voriconazole in the US, at least two guidelines now recommend avoiding voriconazole or making phenotype-specific dosage empirical adjustments (i.e., initiating the dose at 1.5× the standard starting dose) in patients with certain CYP2C19 phenotypes.[14,15] Recent Australian guidelines suggest considering alternate antifungal agents and CYP2C19 testing if a patient has subtherapeutic concentrations after two appropriate dose adjustments.[13]

2.2 | Itraconazole

Therapeutic drug monitoring (TDM) for itraconazole measures concentrations of both the parent drug and its active metabolite, hydroxy-itraconazole. The sum of both itraconazole and hydroxy-itraconazole

TABLE 1 Consensus recommendations for triazole antifungal therapeutic drug monitoring.[13,43,44]

Triazole	PK Considerations	Indications for TDM	Timing of sample in relation to drug initiation or change in steady-state concentration (adults)[a]	Target trough concentrations	Toxicity ceiling for troughs	PD targets (preclinical PK/PD efficacy target for all azoles is AUC_{0-24}/MIC)	Recommendations for dose adjustment
TDM routinely utilized							
Voriconazole	Nonlinear Michaelis–Menten PK, high bioavailability, equivalent dosing between formulations[b]; unpredictable outcome based on dose modifications	All patients, prophylaxis or treatment	Trough, 2–5 days (~2 days with a loading dose, ~5 days without loading dose)	Prophylaxis: ≥0.5 mg/L	4–5.5 mg/L	Aspergillosis: $fAUC_{0-24}$/MIC >25	Dosing algorithms Bayesian software
	Consider CYP2C19 genotyping			Treatment: ≥1–2 mg/L		Cmin/MIC 2–5 mg/L	Practically, dose adjustments are made in increments of 50–100 mg due to tablet size TDM must be performed after dose adjustment since metabolism is nonlinear
Itraconazole	Nonlinear PK, slow drug accumulation with a long half-life, dosing is not equivalent between formulations	Sporanox® capsules: all patients, prophylaxis or treatment	Any point in the dosing interval; however, troughs are most common in clinical practice	Prophylaxis: ≥ 0.5 mg/L	17.1 mg/L (bioassay) 3–4 mg/L (HPLC or LC/MS)	Not established	Sporanox®: 100 mg increments
		Suspension or SUBA-itraconazole capsule (Tolsura®): consider routinely for treatment, recommended with suspension for prophylaxis	~5–7 days with loading dose, 10–14 days without loading dose	Treatment: ≥1 mg/L (These concentration thresholds are based on the itraconazole component only)			Tolsura®: 65 mg increments Solution: 10 mg/mL; 50–100 mg increments

(Continues)

TABLE 1 (Continued)

Triazole	PK Considerations	Indications for TDM	Timing of sample in relation to drug initiation or change in steady-state concentration (adults)[a]	Target trough concentrations	Toxicity ceiling for troughs	PD targets (preclinical PK/PD efficacy target for all azoles is AUC_{0-24}/MIC)	Recommendations for dose adjustment
Posaconazole	Linear PK, high bioavailability, and dosing are not equivalent between formulations	Immediate-release suspension: all patients, prophylaxis or treatment DR tablet, DR suspension, or intravenous: consider routine TDM for treatment, recommended for prophylaxis	Trough 5 days with a loading dose, 7 days without a loading dose	Prophylaxis: ≥0.5–0.7 mg/L Treatment: ≥1–1.5 mg/L	>3–3.75 mg/L	$fAUC_{0-24}$/MIC >25–50	DR tablet: 100 mg increments; doses up to 300 mg BID have been utilized
TDM recommended in specific circumstances							
Fluconazole	Linear PK, high bioavailability, equivalent dosing between formulations	Rarely performed and not routinely recommended. May consider in special populations if concern for clinical failure (e.g., pediatric patients, concern for absorption when used for prophylaxis or treatment, patients receiving CRRT)	Trough 5–7 days (sooner with loading dose)	Not established	Not established	AUC/MIC >25–100 Dose/MIC >50 Cmin 10–15 mg/L	IV, oral: 200 mg increments
Isavuconazole	Linear PK, high bioavailability, equivalent dosing between formulations	Patients receiving alternative methods of administration (e.g., opened capsules via enteral feeding tubes), with drug–drug interactions, critical illness, extremes of weight, refractory/resistant infections, pediatric, or other factors anticipated to alter pharmacokinetics	Any point in the dosing interval; however, troughs are most common in clinical practice ~5–7 days with loading dose, 10–14 days without loading dose	Not established and not routinely utilized for prophylaxis For treatment, no target is established. Some experts consider ≥1–2 mg/L	>4.6–5.1 mg/L	$fAUC_{0-24}$/MIC >25–50	IV, oral: 186 mg increments; doses up to 372 mg BID or 744 mg daily have been reported (186 mg isavuconazonium sulfate = 100 mg isavuconazole)

Abbreviations: AUC, area under the curve; Cmin, minimum concentration; CRRT, continuous renal replacement therapy; DR, delayed release; HPLC, High-performance liquid chromatography; L, liter; LC/MS, Liquid chromatography–mass spectrometry; MIC, minimum inhibitory concentration; mg, milligram; PK, pharmacokinetic; PD, pharmacodynamic.

[a]After drug initiation, dose adjustment, or with the initiation or cessation of an interacting medication. A comprehensive review of triazole drug–drug interactions is outside the scope of this work; key points for possible interactions are outlined in the main text.

[b]Highly bioavailable agent, so dosing between intravenous and oral formulations is 1:1. However, TDM is recommended after switching from intravenous to oral (or vice versa) due to variations in absorption and metabolism (nonlinear PK).

plasma concentrations yields the total bioactive drug concentration, but therapeutic trough targets discussed below are based on itraconazole alone as measured by chromatographic assays (e.g., HPLC, LC/MS), which are more commonly performed than bioassay for clinical samples in the US and Europe. More extensive information is provided in the Appendix S1. TDM is recommended for all patients receiving first-generation itraconazole capsules (Sporanox®) due to unreliable absorption and the likelihood of subtherapeutic concentrations.[16] The need for TDM with the more reliably absorbed oral solution or newer SUBA-itraconazole capsules (Tolsura®) is uncertain; however, clinical data support a trough threshold of >0.5 mg/L when using itraconazole for antifungal prophylaxis. Target attainment with SUBA-itraconazole may be improved over older formulations but could still be suboptimal in certain populations such as lung transplant recipients, in whom only 49% achieved initial trough concentrations >0.5 mg/L with a starting dose of 100 mg twice daily.[17] Similarly, 68% of patients with hematologic malignancies achieved trough concentrations ≥0.5 mg/L after 10 days of SUBA-itraconazole dosing, but high inter-patient variability was apparent.[18]

The target trough concentration for treatment is unclear, although most experts cite a value of >1 mg/L. In general, it is recommended to wait approximately 5–7 days before checking an itraconazole blood concentration (when loading doses are used), and 10–14 days without a loading dose due to the prolonged half-life and slow accumulation to steady state. In theory, concentrations could be checked at any time during the dosing interval due to the long half-life; however, troughs are the most common point of monitoring utilized in clinical practice. If reporting trough itraconazole concentrations via bioassay, it might be reasonable to consider 17 mg/L as the toxicodynamic threshold to consider lowering a patient's itraconazole dose. Conversely, a lower toxicity threshold (i.e. 3–4 mg/L) should be considered if itraconazole trough concentrations are measured by chromatographic assays. Clinicians should be vigilant for signs and symptoms of pseudohyperaldosteronism (e.g., new or worsening hypertension, hypokalemia) in patients receiving itraconazole therapy. Finally, TDM is recommended when interacting drugs start or stop (either inhibiting absorption or affecting metabolism), concerns for patient adherence or gastrointestinal absorption exist, and/or the patient has manifestations of toxicities.

2.3 | Posaconazole

The need for routine TDM during posaconazole prophylaxis or treatment is principally driven by the variable bioavailability of oral formulations. Multiple studies have reported subtherapeutic troughs (<0.7 mg/L) in a high proportion of patients receiving the immediate-release posaconazole suspension.[19,20] In contrast, fewer than 10% of patients enrolled in clinical studies utilizing the delayed-release (DR) tablet or IV formulations of posaconazole were reported to have serum posaconazole troughs below 0.5 mg/L.[21–24] Although some observational studies have confirmed a low prevalence of subtherapeutic posaconazole trough concentrations in patients receiving the newer formulations, others have reported up to one-third of patients receiving DR tablets still exhibit low systemic exposures, especially in those with poor appetite, concomitant acid-suppression therapy, and severe diarrhea/intestinal mucositis.[25–29] Recently, centers have crushed DR tablets for patients with enteral feeding tubes to avoid the need for a central venous catheter for intravenous posaconazole administration; TDM is recommended if employing this dosage form modification.[30]

The concentration-effect relationship of serum posaconazole exposures and mycological outcome in vivo is well established from animal models and limited observational data in humans.[31] However, there is a lack of data from prospective randomized trials to demonstrate a specific correlation of clinical outcomes based on target attainment with posaconazole in the treatment of IFIs.[32] TDM data from a recent clinical trial of posaconazole versus voriconazole for invasive aspergillosis have yet to be published.[24] From a toxicodynamic standpoint, accumulating clinical experience with the new posaconazole formulations has suggested higher rates of hepatotoxicity and pseudohyperaldosteronism are possibly linked to elevated posaconazole serum exposures.[33]

Routine TDM should be implemented for all patients receiving immediate-release posaconazole suspension. For dosage forms with more reliable bioavailability (e.g., DR tablet, DR suspension, IV), decisions regarding whether TDM should be performed routinely in all patients or selectively targeted to patients with IFIs and/or specific risk factors (e.g., GI dysfunction, obesity, drug interactions) will largely depend on resources, expertise, and patient population at individual centers for performing, interpreting and applying TDM results in daily patient care. Conditions that strongly favor TDM include patients with risk factors for poor absorption (e.g., GI dysfunction), resistant/refractory infection, evidence of toxicity (e.g., signs of pseudohyperaldosteronism, hepatic injury), physiologic abnormalities, drug interactions, etc. When TDM is performed, a posaconazole trough should be measured at a steady state (approximately 5 days after initiation if a loading dose is used; a trough should be drawn 7 days after dosage adjustment, initiation or discontinuation of an interacting medication, or initiation without a loading dose).

2.4 | Fluconazole

Currently, there is a lack of evidence to support routine TDM for fluconazole. In limited scenarios such as the critical care setting, some groups have recommended TDM to optimize the probability of obtaining the maximal fluconazole pharmacokinetic/pharmacodynamic (PK/PD) target of AUC/MIC > 100.[34] These authors suggest steady state sampling times at 1, 4, and 24 h to estimate the AUC. However, trough concentrations correlate reasonably well with AUC.[35] A trough concentration target of 10–15 mg/L as a surrogate for AUC/MIC > 100 (based upon a MIC value of 0.125) has been suggested for clinical practice in liver transplant patients.[36] There is no established toxicodynamic threshold for fluconazole.

TDM is not routinely recommended for adults receiving fluconazole therapy, regardless of formulation or route of administration. The benefit of TDM has not been demonstrated in clinical studies, and pharmacokinetics are most often predictable and linear. In clinical scenarios of known pharmacokinetic variability (e.g., critical illness), use of appropriate weight-based dosing accounting for renal function or renal replacement therapy (e.g., 400 mg twice daily as a maintenance dose in a 70 kg critically ill patient on CRRT with candidemia) is likely acceptable without the need for TDM. Fluconazole TDM may be reasonable in pediatric patients with anatomical considerations, physiologic abnormalities, or drug interactions potentially impacting fluconazole concentrations.

2.5 | Isavuconazole

In randomized, clinical trials, >90% of patients achieved trough concentrations >1 mg/L, and no concentration-dependent relationship was observed for efficacy or safety.[37,38] Therefore, routine TDM of isavuconazole was not initially recommended for most patients. However, patients receiving isavuconazole through alternative methods of administration (e.g., opened capsules via enteral feeding tubes), with drug–drug interactions, critical illness, extremes of weight, refractory/resistant infections, or other factors anticipated to alter pharmacokinetics may benefit from plasma concentration monitoring.[39–41] Some experts recommend maintaining a trough concentration >1 mg/L for efficacy, despite no established pharmacodynamic target.[42] Additionally, a threshold of 4.6–5.1 mg/L is emerging as a potential safety target, with higher concentrations resulting in more gastrointestinal toxicity. Due to the prolonged half-life of isavuconazole, if TDM is utilized, a concentration could theoretically be sampled at any point in the dosing interval once a patient has achieved a steady state (approximately 5–7 days with a loading dose and 10–14 days without a loading dose). Routine TDM for isavuconazole is not recommended except in situations of known pharmacokinetic variability and/or refractory/resistant infections where higher concentrations may be desired. TDM for isavuconazole may be reasonable to perform in children, especially those receiving treatment for a resistant/refractory infection and/or with anatomical considerations, physiologic abnormalities, or drug interactions that may alter isavuconazole concentrations.

3 | CONCLUSIONS

The SIDP supports routine TDM in adult patients receiving voriconazole, itraconazole, and posaconazole, and TDM in certain circumstances for fluconazole and isavuconazole. For pediatric patients, there may be additional considerations for the timing of levels and dosing due to altered pharmacokinetics, but the general concepts for TDM goals are also applicable in this population. Facilities should ensure access to timely plasma concentrations where appropriate and consider quality improvement initiatives to optimize triazole TDM in their practice setting.

AUTHOR CONTRIBUTIONS

Dr. McCreary and Johnson take full responsibility for the integrity and accuracy of the manuscript. All authors were involved with concept and design, literature review, interpretation of available data, drafting of the manuscript, and critical revision of the manuscript.

ACKNOWLEDGMENTS

The authors acknowledge the Society of Infectious Diseases Pharmacists Publications and Podcast Committee for their critical review of this manuscript.

CONFLICT OF INTEREST STATEMENT

Dr. Andes has received consulting fees from Astellas, Roche, Merck, SFunga, and Amplyx, research grants to his institution from sFUnga, Biosergen, Amplyx, and the National Institutes of Health, and patents for turbinmicin, forazoline, and cyphomycin. Dr. Cattaneo has received consulting fees from Pfizer and Viiv Healthcare, and honoraria from Janssen Cilag and Merck, Sharp & Dohme. Dr. Davis has received consulting fees from Shionogi and Ligand Pharmaceuticals and honoraria from Ligand Pharmaceuticals. Dr. Johnson has received consulting fees from Astellas, Merck, Entasis, Pfizer, and Theratechnologies, author royalties from UpToDate, research grants to her institution from Astellas, Scynexis, Charles River Laboratories, and Merck & Co, and has a patent pending for gene expression-based classifiers of fungal infection, outside the submitted work. She is also on the Board of the Society of Infectious Diseases Pharmacists. Dr. Lewis has received consulting fees from F2G, Gilead, Scynexis, and the British Society for Antimicrobial Chemotherapy, honoraria from Pfizer, Avir, and Gilead, and author royalties from UptoDate. He has also received research grants to his institution from Merck & Co and the European Society for Clinical Microbiology & Infectious Diseases, and materials (antifungal powder) to his institution from Pfizer. Dr. McCreary has received consulting fees from Cidara, Ferring, Summit, LaJolla, Merck, AbbieVie, Shionogi, MeMEd, Entasis, and LabSimply and speaker honoraria from Shionogi. Dr. McCreary has also served on the Board of the Society of Infectious Diseases Pharmacists. Dr. Narayanan has received honoraria from Astellas and Beckman Coulter. Dr. Watt received research grants from NIH and is a member of the American Academy of Pediatrics Committee on Drugs. Dr. Wiederhold has received research grants from Astellas, bioMerieux, F2G, Maxwell Biosciences, Mycovia, and sFunga outside of the submitted work, honoraria from the American Society for Microbiology, Mycoses Study Group Education and Research Consortium, and the Infectious Diseases Society of America and served on an advisory board for F2G. He has received meeting/travel support from Fungal Diagnostics Laboratory Consortium and Clinical Laboratory Standards Institute. He has received materials (antifungal powder) from Cidara, F2G, Mycovia, Pfizer, and Scynexis. All other authors report no report disclosures, conflict

of interest, or relevant financial interests related to the content of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: McCreary EK, Davis MR, Narayanan N, et al. Utility of triazole antifungal therapeutic drug monitoring: Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2023;43:1043-1050. doi:10.1002/phar.2850