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ADVANCES IN DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS (O MORRISSEY, SECTION EDITOR)

Azole Therapeutic Drug Monitoring and its Use in the Management of Invasive Fungal Disease

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Abstract

Purpose of review This article summarises the pharmacologic rationale for therapeutic drug monitoring (TDM) of azoles in the management of invasive fungal disease (IFD), explores practical recommendations for TDM guided dosing, discusses barriers to TDM and highlights future directions and challenges to incorporating azole TDM into routine clinical practice.

Recent findings Pharmacokinetic studies have demonstrated that significant inter- and intra-patient variability exists in the exposure of azole antifungal agents. This variability can affect treatment success and contribute to toxicity. TDM has been proposed as a tool to individualise azole dosing to optimise efficacy and reduce toxicity. Accounting for significant heterogeneity, there is evolving evidence that TDM improves clinical outcomes for itraconazole, voriconazole and posaconazole. TDM for fluconazole and isavuconazole requires further evaluation.

Summary There remains ambiguity over the optimal approach to performing, interpreting, and utilising TDM to improve patient outcomes. This is attributable to a relative lack of literature, operational and logistical challenges to performing TDM.

Keywords Antifungal agents · Pharmacokinetics · Pharmacodynamics · Dose-exposure relationships

Introduction

Invasive fungal diseases (IFD) are associated with significant morbidity and mortality [1]. At-risk populations include patients with solid-organ or stem-cell transplantation, malignancies, chronic lung disease and critically ill intensive care unit patients; however, IFD can occur in patients with numerous other comorbidities [1]. Triazole antifungal agents (triazoles) play a key role in the management of IFD. Studies have demonstrated considerable intra- and inter-patient variability in azole pharmacokinetics (PK) [2, 3]. Such alterations in PK can lead to variability in azole exposure [4••]. This variability in exposure can pose the risk of toxicity or treatment failure [4••, 5••].

Therapeutic drug monitoring (TDM) by way of measuring serum azole concentrations and subsequent dose adjustment to achieve desired target concentrations is a useful tool in overcoming this variability. TDM has been shown to be particularly useful in the context of triazoles with narrow therapeutic indices and/or unpredictable PK parameters such as voriconazole, posaconazole and itraconazole [6, 7•, 8]. Significant institutional and inter-physician variability exists in the application, interpretation, and utilisation of azole TDM [9]. This is driven by the lack of robust prospective data on the clinical outcomes [9]. Moreover, the utility of TDM for other triazoles such fluconazole and isavuconazole remains to be explored. Other barriers include lack of assays, unfavourable testing and turnaround times and lack of expertise and infrastructure [7•]. In this review we will discuss the PK and pharmacodynamic (PD) properties of azole antifungals with a specific focus on triazoles and discuss the evidence and rationale for triazole TDM.

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Azole antifungal agents

Azole antifungals are divided into two subclasses. The imidazoles (ketoconazole, clotrimazole) contain a heterocyclic five-member ring with two nitrogen atoms. The triazole group contain three nitrogen atoms. Azole antifungals exert their fungistatic activity by inhibiting the enzyme, 14-α-demethylase enzyme, which is required for the conversion of lanosterol to ergosterol leading to accumulation of toxic precursors. The 14-α-demethylase enzyme belongs to the cytochrome-P-450 (CYP) family. Azoles also inhibit other isoenzymes of the CYP system resulting in numerous drug interactions [10•]. Triazoles approved for use in the management of IFD include fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole.

Azole antifungals with most evidence for therapeutic drug monitoring

Itraconazole, posaconazole and voriconazole have the most evidence for TDM currently. The indications, target concentrations and toxicity thresholds are discussed in Table 1

Itraconazole

Spectrum of activity

Itraconazole is active against numerous dermatophytes, yeasts, and Aspergillus spp. [13]. It is indicated in the treatment of onychomycosis, blastomycosis, histoplasmosis, coccidioidomycosis and as salvage therapy for aspergillosis [32]. Pertinent side-effects include gastrointestinal (GIT) symptoms, hepatotoxicity, peripheral neuropathy and should be avoided in congestive heart failure [33].

Pharmacokinetics and pharmacodynamics of itraconazole

Itraconazole is available in capsule, oral suspension, tablet and intravenous (IV) formulations. These formulations are not interchangeable. The absolute oral bioavailability is 40–60% [10•]. Absorption from capsules is dependent on gastric acidity, food intake and gastric transit times [13]. Itraconazole is highly lipophilic and protein-bound (99.8%), has a large volume of distribution (V_d) of 11 L/kg, and has a $t_{1/2}$ of ~ 30 h [10•]. The variable absorption, non-linear PK, poor solubility, off-putting taste, and GI intolerance can lead to variability of serum concentrations [12•, 13]. Its active metabolite, hydroxy-itraconazole, has comparable in vitro antifungal activity to itraconazole [10•, 34]. Although this bears little clinical significance, the presence of hydroxy-itraconazole may result in measurement discrepancies of serum itraconazole concentrations. The newest capsule formulation called SUBA (Super-bioavailable), has a superior relative bioavailability of 173% compared to conventional capsules and less inter-patient variability [35]. The PD drug exposure target is quantified in terms of trough concentration (C_{min}) rather than AUC (or AUC/MIC ratio). A C_{min} range of 0.5–1 mg/L (measured using HPLC/mass spectrometry) is generally accepted [12•]

Drug–drug interactions

All formulations undergo extensive hepatic metabolism by the CYP3A4 isoenzyme, and CYP3A4 is inhibited by itraconazole itself. Thus, altered hepatic metabolism and co-administration of CYP inducers/inhibitors may contribute to variabilities in exposure and efficacy [14].

Itraconazole therapeutic drug monitoring

Although inter- and intra-patient variability of serum itraconazole has been demonstrated, the clinical impact of performing TDM is sparse [36]. Clinically relevant drug exposure–response relationships and exposure–toxicity relationships are recognized for itraconazole [17].

Clinical efficacy

Improved outcomes have been noted with trough concentrations of 0.25–0.5 mg/L when using itraconazole as prophylaxis for IFD in neutropenic patients and target of > 0.25 mg/L for prophylaxis is supported by two meta-analyses [5••, 15]. This finding differs from the target thresholds of 0.5–1.0 mg/L suggested in published guidelines [11•, 12•, 37–39].

For IFD treatment, a meta-analysis demonstrated that a target trough concentration of > 0.5 mg/L was associated with increased treatment success [5••], whilst a concentration of > 1 mg/L was deemed appropriate in an alternate study [16]. Similar targets are recommended by the British Society for Medical Mycology (BSMM); higher threshold of > 1 mg/L is supported in other published guidelines [12•, 37, 38]. The IDSA Aspergillosis guideline uniquely identifies an additional treatment goal of combined itraconazole and hydroxyl-itraconazole trough > 1.5 mg/L [40]. These targets have been derived almost exclusively from immunocompromised populations and evidence for their other populations is limited [13].

Table 1 Azoles with most evidence for TDM

Indications for TDM	Altered PK	Drug interactions	Sample timing	Target range	Toxicity threshold	Dose adaptation
Itraconazole						
Routine for treatment irrespective of formulations [11•] Routine for prophylaxis with itraconazole capsule and oral solution Selected cases at risk of low exposure receiving *SUBA®- itraconazole prophylaxis (e.g., drug–drug interactions) [11•] Patients who initiate or discontinue interacting medications, undergo a change in formulations or dosing, or demonstrate a lack of response or signs of toxicity [11•]	Yes; Factors leading to PK variability include gastric pH, variable absorption, non-linear PK, poor solubility, off-putting taste, and **GIT symptoms [12•, 13]	Yes; CYP3A4 inhibitors [14]	Timing: 5–7 days (loading dose) 10–14 days (no loading dose) [12•] Thereafter, every 1–2 weeks if steady state achieved [4••]	Prophylaxis: > 0.25–0.5 mg/L [5••, 15] Treatment: > 1–1.5 mg/L [16]	3–5 mg/L [17] **GIT toxicity most common	Lack of evidence-based guidelines on dose adaptation Ensuring adherence, checking for drug interactions, change of formulation from capsules to liquid, ensuring each formulation is taken appropriately in relation to food (capsule with food and liquid on empty stomach) or changing to *SUBA®-itraconazole [4••]

Table 1 (continued)

Indications for TDM	Altered PK	Drug interactions	Sample timing	Target range	Toxicity threshold	Dose adaptation
Voriconazole						
Routine for treatment [11•] Limited evidence for routine use in prophylaxis	Yes; Factors leading to ^^PK variability include: Non-linear ^^PK, saturable metabolism, variable absorption in disease states and genetic polymorphisms [10•]	Yes; Inhibitor and substrate for CYP2C19, CYP2C9 and CYP3A4	Timing: Within 2–5 days of initiating therapy. [12•] Repeat testing at 3–5 days may be warranted in; critically unwell patients, those suspected of therapeutic failure, drug interactions or a change in dosing; [4••]	Prophylaxis: nil established Treatment: > 1.7 – 2 mg/L; > 2 mg/L if high risk, poor prognosis, or bulky disease [2, 18, 19, 20••, 21••]	4–6 mg/L [21••] Routine monitoring of ^LFTs and clinical signs of neurotoxicity are also recommended	Assessment of adherence and drug interactions affecting voriconazole metabolism should occur TDM guided dose-adjustment algorithms have been evaluated [22•] • < 0.6 mg/L – increase by 100 mg, recheck trough day 5 • 0.7 – 0.9 mg/L – increase by 50 mg, recheck trough day 5 • 1- 4.0 mg/L – no change • 4.1 – 5.5 mg/L – dose reduced by 50 mg, recheck day 5 • 5.6 – 7.9 mg/L – hold dose, recheck daily troughs, restart at 100 mg less when trough ≤ 2.5 mg/L and recheck at day 5 • ≥ 8.0 mg/L – hold dose, recheck daily troughs, restart at 50% reduced dose when trough ≤ 2.5 mg/L
Posaconazole						
Routine for treatment [23] Routine for prophylaxis with suspension [11•] Selected cases at risk of low exposure receiving ˜DRT formulation for prophylaxis Not required for #IV formulation	Yes; For oral suspension factors include highly variable absorption, gastric pH, and high-fat meals No; For ˜DRT and #IV formulations	Substrate for ∅UGT enzymes Substrate for ⊕P-gp transporter Potent inhibitor of CYP3A4 [24]	Timing: 7 days post administration [25, 26]	Prophylaxis: > 0.5 mg/L [24, 27, 28] Treatment: > 1.0 – 1.25 mg/L [23]	⊗PIPH associated with concentrations > 4 mg/L [29] Concentrations less established for other adverse effects [30••]	Lack of evidence-based guidelines on dose adaptation [31]

*SUBA: Super bio-available itraconazole; **GIT: gastrointestinal; ^LFTs: Liver function tests; ^^PK: pharmacokinetics; ~DRT: Delayed release tablet; #IV: Intravenous; ⊗PIPH: Posaconazole induced pseudo-hyperaldosteronism; ∅UGT: UDP-glucuronyl-transferase; ⊕P-gp: P glycoprotein; mg/L = milligrams per litre

Clinical toxicity

A retrospective cohort study conducted on 216 patients identified that 45.8% experienced an adverse event, of whom 33% required cessation of therapy [17]. A logistic regression analysis revealed a progressive increase in the probability of toxicity with increasing concentration and identified that 86% of patients with serum concentrations > 17.1 mg/L (via bioassay) developed toxicity [17]. Based on this study, the upper limit for toxicity has been identified to range between 3-5 mg/L (via HPLC) [12•, 40]

Issues and barriers with itraconazole TDM

The studies conducted to establish ideal concentration targets are predominantly retrospective with small case numbers, did not have standardized reasons or methods for obtaining concentrations and were not inherently designed to establish the ideal concentration targets [13]. These issues highlight the heterogeneity of publications in the field and limit the results of these studies from being generalizable. The measured concentration is dependent on the assay method i.e., bioassays typically measure both hydroxyitraconazole and itraconazole and consequently the concentrations can be 2–sevenfold higher than those measured by HPLC alone [41]. Itraconazole concentrations should be measured independent of its metabolites, via high performance liquid chromatography (HPLC) assays [12•, 37, 38, 40, 42]. The therapeutic targets for TDM of itraconazole evolved when there was little established triazole resistance [4••]. The appropriate C_{min} targets for isolates with non-wild-type MICs is unknown. It is unclear if isolates with elevated MICs can be treated with dosage escalation in clinical settings [43]. Further research in this area is warranted [39]. Finally, evidence for TDM for newer formulations for SUBA capsules needs to be established.

Voriconazole

Spectrum of activity

Voriconazole portrays a broad spectrum of antifungal activity and remains the first-line option for invasive aspergillosis [40]. An AUC/MIC > 25–32 or a trough/MIC 1–5 are associated with clinical efficacy and patient survival [44, 45]. It is available in tablet, solution, and intravenous formulations.

Pharmacokinetics and pharmacodynamics of voriconazole

Voriconazole bioavailability amounts to 96% and is independent of gastric pH [10•]. However, its absorption is significantly decreased in disease states, such as in the lung transplant population where bioavailability ranges from 24–63% due to the gastrointestinal complications experienced post-transplant [46]. Considerable variability in serum concentrations were also seen in critically ill patients [47]. 58% is protein-bound, whilst V_d measures ~ 4.5 L/kg. It undergoes hepatic phase I biotransformation involving CYP2C9, CYP2C19 and CYP3A4. Genetic polymorphisms of CYP2C9 and 2C19 lead to ultra-rapid and poor-metabolizer phenotypes, further contributing to variations in serum concentrations [10•, 48]. Due to non-linear, saturable metabolism, the half-life is dose-dependent with an apparent $t_{1/2}$ of ~ 6 h at standard dosage that increases with the serum concentration [10•, 49]. Patients with liver disease may experience altered metabolism of voriconazole thereby prolonging the $t_{1/2}$ [50]. An AUC/MIC ratio > 25–32 is the key PK/PD parameter that underpins clinical efficacy [19, 21••].

Drug–drug interactions

Voriconazole is a strong inhibitor of CYP2C19, CYP2C9 and a moderate inhibitor of CYP3A4 but also a substrate for CYP2C19, CYP2C9 and CYP3A4. Proton pump inhibitors, glucocorticoids and rifampicin are all implicated in increasing or decreasing voriconazole concentrations [51].

Voriconazole therapeutic drug monitoring

Voriconazole exhibits a clear exposure–response relationship, has a narrow therapeutic range, and has substantial interpatient PK variability [52]. In addition, genetic factors, gastrointestinal absorption, and drug interactions impact clinical response [49]. Its non-linear PK result in a disproportionate increase in serum level at higher doses [45]. Consistent adoption of guidelines is required to improve ordering and interpretation of voriconazole TDM [53, 54].

Clinical efficacy

Studies on voriconazole TDM have been limited and largely observational with significant methodological variations [20••, 21••, 55, 56]. An RCT of 110 patients demonstrated that patients in the TDM arm had greater rates of complete or partial response (81% vs 57%) and lower rates of drug discontinuation (4% vs 17%) when compared with controls [57]. This result was replicated in a retrospective comparison of 216 critically ill patients, with the TDM group having a significantly higher rate of response than the control arm [58••]. A meta-analysis of 24 studies identified that 72.4% of patients had a successful outcome if therapeutic concentrations of voriconazole were achieved [21••]. Targeting trough concentrations of 1.5–4.5 mg/L has led to similar outcomes

as targeting AUC/MIC parameters on three previous meta-analyses and a systematic review [18, 19, 20••, 21••]. A multi-centre, retrospective cohort analysis identified that concentrations < 1.7 mg/L were associated with treatment failure [2]. An observational study of 52 patients established that TDM was paramount in maintaining therapeutic trough concentrations [59], whilst a retrospective cohort study observed a 42% decrease in treatment failure when trough concentrations were maintained through TDM [60].

Clinical toxicity

Published guidelines suggest an upper limit of 4-6 mg/L to minimize toxicity [11•, 12•, 18, 37, 40]. This is supported by a meta-analysis that identified patients with supratherapeutic voriconazole serum concentrations (4.0–6.0 mg/L) were at increased risk of toxicity (OR 4.17; 95% CI 2.08–8.36) with a threshold > 6.0 mg/L on a pooled analysis being most predictive of toxicity (OR 4.60; 95% CI 1.49–14.16) [21••]. A retrospective study of critically ill patients on voriconazole identified that the incidence of adverse events was lower when TDM was performed (19.8% vs 9.6%; P = 0.033) [58••]. Whilst visual disturbances are dose-dependent, neurotoxicity has been commonly seen with trough concentrations greater than 4–5.5 mg/L [2, 55, 59]. Although hepatotoxicity is common and appears dose-dependent, there are no consensus threshold to predict its risk [55]. TDM directed dose adjustment has resulted in improvement of hepatotoxicity in two studies [61, 62]. The above highlights the utility of TDM in reducing drug toxicity.

Issues and barriers with voriconazole TDM

Clinical application

Although voriconazole TDM has been shown to improve efficacy and toxicity outcomes as above, the findings of above studies are variably incorporated into published guidelines [12•, 18, 37, 40]. Given the methodological inconsistencies across these studies, some experts have cautioned against universal utilisation of TDM and instead reserve use for those experiencing therapeutic failure or toxicity [56, 63]. Additionally, there is limited evidence to suggest routine TDM for voriconazole prophylaxis [64]. However, a prospective study has shown improvement in target concentration attainment through TDM and consequently low rates of breakthrough infection [22•].

Clinical resistance and treatment failure

An array of mutations conferring azole resistance have been described and commonly involve modification of the cyp51A gene [65]. Higher exposures to voriconazole are required to achieve the same clinical outcomes compared with wild type Aspergillus fumigatus [65]. The elucidation of optimal AUC/MIC ratios to predict treatment success in azole-resistant strains remains a challenge [66]. Trough/MIC ratios (C_{min}/MIC) have been suggested instead of trough concentrations in azole-resistant isolates [45, 59]. Population PK studies have identified a C_{min}/MIC of 2–5 to be associated with a near-maximal probability of response [45, 52, 59]. Treatment failure can occur despite therapeutic concentrations due to various confounders of disease severity, host physiology and variable target tissue penetration [49]. Further, poor compliance with guidelines for voriconazole dosing and monitoring have been reported, reflecting habitual prescribing [54].

Genotype polymorphisms

A meta-analysis identified 10 studies examining the association between genetic polymorphisms and therapeutic outcomes. Overall, no significant relationship was found between CYP2C19 polymorphisms and efficacy or with toxicity [20••, 67]. A prospective study of 263 patients with acute myeloid leukaemia was CYP2C19 genotyped before receiving prophylactic voriconazole. Higher prophylactic doses were recommended for rapid metabolisers. This approach led to avoidance of subtherapeutic concentrations but had no impact on efficacy or toxicity [68]. Higher rates of treatment success (78% vs 54%, P < 0.001) were observed, in comparison with historical controls, in a study where the dosing regimen was guided based off an individuals' CYP2C19 genotype [69]. Recommendations for managing patients with CYP2C19 mutations and for CYP2C19-guided voriconazole dosing exist [70, 71]. However, validation of these recommendations is pending [20••].

Posaconazole

Spectrum of activity

Posaconazole has a wide spectrum of activity and is licensed for prophylaxis in high-risk haematological populations and for treatment of invasive aspergillosis [72–74].

Pharmacokinetics and pharmacodynamics of posaconazole

Posaconazole was previously available only as an oral suspension displaying highly variable absorption, with bioavailability limited by gastric pH and requiring intake of high-fat meals [75, 76]. This formulation experiences saturable enteral absorption therefore requiring increased frequency and split dosing regimens [77]. More recently,

gastro-resistant, and delayed-release tablet/capsule (DRT) formulations and IV solutions are available. Compared to the suspension, DRT eliminates the need for food or multiple daily dosing to achieve adequate systemic exposure and its bioavailability is unaffected by gastric pH or motility [78, 79]. Compared to suspension, DRT had substantially higher exposure and less variability in bioavailability with mean $t_{1/2}$ values being similar (23.1 h for DRT and 29.2 h for suspension), whilst clearance was slower (~ 9 l/h versus ~ 34L/h) [80]. Intake of high-fat meals with DRT did not result in a significant change in exposure [81]. Both formulations are highly protein-bound [75]. The IV solution needs to central line access for administration and meets the exposure targets with its PK being dose-proportional [82].

Drug–drug interactions

Posaconazole is barely metabolised by the CYP P450 pathways. ~ 17% undergoes glucuronidation by UDP-glucuronyl-transferase (UGT) 1A4 with the remainder eliminated unchanged [83]. Posaconazole can be impacted by drugs that interact with UGT enzymes like phenytoin and rifampicin. Posaconazole is a substrate for P-glycoprotein and co-administration of inducers (e.g., rifampicin) or inhibitors (e.g., verapamil) may affect serum concentrations. Posaconazole remains a potent inhibitor of CYP3A4 [24].

Posaconazole therapeutic drug monitoring

A lack of consensus guidelines regarding posaconazole TDM results in frequent misinterpretation, inconsistent follow-up of concentrations and is compounded by inappropriate requesting highlighting the need for a standardized approach [84].

Clinical efficacy

The recommended target concentrations are > 0.5–0.7 mg/L for prophylaxis and > 1–1.25 mg/L for treatment of IFD using Posaconazole [11•, 25, 39, 42, 66, 85]. TDM is recommended for oral suspension formulation particularly in the case extremes of body weight or if toxicity or drug interaction is suspected [25, 86, 87].

While current recommendations, supported by a recent meta-analysis, do not recommend routine posaconazole TDM with DRT/IV formulation used for prophylaxis [42, 88, 89], a cohort analysis of 77 HSCT patients revealed significant intra- and inter-patient variability of DRT trough concentrations [90••]. An additional longitudinal analysis revealed posaconazole concentrations were frequently outside the therapeutic window [31]. A further study highlighted that exposure may remain variable in those weighing > 90 kg and in patients with diarrhoea [91].

Exposure–response relationship for treatment has been demonstrated in previous studies with average concentrations (C_{avg}) correlating with clinical efficacy [25]. A single centre study has identified significant interpatient variability with DRT when utilized for treatment in a lung transplant population with 73% requiring dose adjustments to reach targets [92]. The sum of the above suggests that there remains a role for performing TDM even when newer formulations of posaconazole are utilized.

Clinical toxicity

Gastrointestinal side effects, hepatotoxicity, pseudo-hyperaldosteronism, alopecia, and QTc-interval prolongation have been described with posaconazole [29, 75, 93]. However, no clear exposure–toxicity relationship has been established [27, 66]. A retrospective analysis identified 19% of patients with grade 3 or 4 liver injury secondary to posaconazole [30••]. Amongst those who had TDM performed in this study, there was no statistical difference in the median posaconazole concentrations for patients with or without hepatotoxicity (1.765 mg/L versus 1.310 mg/L; P = 0.06). On classification and regression analysis, serum concentrations of ≥ 1.83 mg/L was found to correlate with hepatotoxicity (odds ratio [OR], 5.6 [95% confidence interval [CI], 1.7 to 18.3]; P = 0.005) [30••]. A retrospective cohort analysis identified posaconazole induced pseudo-hyperaldosteronism (PIPH) in 23% of patients on prophylaxis. Patients with PIPH had significantly higher median serum posaconazole concentrations than patients without PIPH (3.0 vs 1.2 µg/mL, P < = 0.000; all patients with posaconazole concentrations ≥ 4.0 µg/mL were diagnosed with PIPH. Development of PIPH in patients with serum posaconazole concentrations < 2.0 µg/mL was uncommon [29]. Further study is warranted to clarify exposure–toxicity relationships.

Issues and barriers with posaconazole therapeutic drug monitoring

Elevated MIC organisms

Posaconazole exposure correlates linearly with the dose; thus, a higher dose of the azole is required to achieve similar efficacy when azole-resistant strains are present [94]. A target trough level of > 1.8 mg/L has been suggested for resistant isolates and TDM should be utilised to achieve these targets [94].

Tissue penetration and impact of TDM

Pulmonary alveolar posaconazole concentrations are 40-fold higher compared to serum concentrations [95]. This may explain the rates of breakthrough infections being only

1.9%–3.9% [27, 28, 72]. TDM still remains a useful intervention in this scenario as it enables detection prolonged sub-therapeutic exposure that can be associated lowered intracellular and pulmonary concentrations [93].

Azole antifungals with emerging evidence for therapeutic drug monitoring

The indications, target concentrations and toxicity thresholds are poorly established for Fluconazole and Isavuconazole and shown in Table 2.

Fluconazole

Spectrum of activity

Fluconazole is cheap, well tolerated and remains a key agent in the treatment of infections with Candida spp. [10•, 37].

Pharmacokinetics and pharmacodynamics of fluconazole

Fluconazole is highly soluble in water, displays excellent bioavailability (> 90%) and enteral absorption is not significantly influenced by food intake or gastric pH [10•]. It is poorly protein-bound (~ 12%) and has a $t_{1/2}$ of 30 h, thus taking 6 days to reach steady-state unless a loading dose is utilized. It has a small V_d of 0.75L/kg and is extensively eliminated by the kidneys. It undergoes linear PK without a significant variability in dose exposure [99]. Fluconazole demonstrates a well-documented dose–response relationship with AUC/MIC > 50 associated with improved treatment outcomes [100, 101].

Drug–drug interactions

Fluconazole is a strong inhibitor of CYP 3A4 and CYP 2C9, thereby leading to numerous drug interactions [10•].

Fluconazole therapeutic drug monitoring

Fluconazole TDM is usually not pursued due to its excellent bioavailability, linear PK, and lack of exposure–response variability. Certain patient populations may still experience unpredictable exposure–response relationships [8, 97••]. However, pursuing TDM in these subsets of patients was limited by lack of clear targets to guide TDM, as most PD data establishing exposure–response relationships utilizes AUC/MIC, which is not a clinically practical parameter for use in TDM [100, 101].

More recently, C_{min} have been shown to correlate with AUC measurements for fluconazole [96••, 97••] with target

Table 2 Azoles with emerging evidence for therapeutic drug monitoring

Agent and indications	Altered PK	Drug interactions	Sample	Target range	Toxicity threshold	Dose adaptation
Fluconazole						
Consider in select circumstances for IFD treatment: [8, 96••, 97••] • Critically ill • Renal replacement • ^CNS infection • Treatment failure	Only in select populations e.g., haemodialysis, critically ill	Strong inhibitor of CYP 3A4 and CYP 2C9	Optimal timing unclear	*C_{min} of 10-15 mg/L (or **AUC/MIC > 50). However, not well elucidated (102)	Nil established	Nil established
Isavuconazole						
Consider in select circumstances for IFD treatment [111, 112••] o Critically ill o Renal replacement o ^CNS infection o Treatment failure o #GvHD o ~ECMO o Obesity	Only in select populations e.g., renal replacement, ECMO, obesity	Substrate for ^^UGT and CYP3A4 Moderate CYP 3A4 inhibitor	Single trough isavuconazole level once steady state has been reached (2–3 weeks) [98] Value of repeat testing unclear [4••]	Not well elucidated	5 mg/L, however not consistently demonstrated	Nil established

*$C_{min:}$ Minimum/trough concentration; **AUC/MIC: Area under the curve/Minimum inhibitory concentration; ^CNS: Central nervous system; #GvHD: graft versus host disease; ~ECMO: Extracorporeal membrane oxygenation; ^^UGT: UDP-glucuronyl-transferase; mg/L = milligrams/litre

AUC/MIC > 50 corresponding to a C_{min} of 10-15 mg/L [102]. Additionally, there is significant inter and intra-patient variability in fluconazole serum concentrations, particularly in critically ill patients or those on dialysis where 30–50% of study population did not reach PK/PD targets, attributing to the altered volume of distribution and clearance in these patients [8, 96••, 97••]. Further, low trough concentrations (< 11 mg/L) were associated with negative treatment outcomes in a cohort of high-risk liver transplant patients in a centre that utilized TDM guided dosing [103]. A cross-sectional study identified a poor correlation between antifungal dosage and serum concentrations and showed that attaining the on-target serum antifungal concentrations was significantly associated with a favourable clinical outcome [104]. Although it is usually well-tolerated, hepatotoxicity and prolonged Qtc interval are harmful adverse effects. There have been no accepted serum concentrations that consistently correlate with systemic toxicity.

Currently, there are significant gaps in the literature with regards to the clinical utility of fluconazole TDM and its routine use is not recommended [11•]. Additionally, access to fluconazole assays is currently restricted to institutions where infrastructure and expertise exist [85]. Interpretation of concentrations and dose adaptation algorithms warrant further study.

Isavuconazole

Spectrum of activity

Isavuconazole has a chemical structure like fluconazole and voriconazole. The active drug is cleaved by serum esterases from its water-soluble prodrug isavuconazonium sulphate [10•]. Isavuconazole has a broad-spectrum of activity against most yeasts and moulds [105]. Its toxicity profile is similar to fluconazole [105].

Pharmacokinetics and pharmacodynamics of isavuconazole

Isavuconazole is available in intravenous and oral formulations. The oral bioavailability is ~ 98% and is extensively protein-bound (98–99%) with a large V_d (300-500L) [10•]. Both formulations have considerably long half-lives that range from 56 to 98 h following oral dosing and 76 to 117 h post IV dosing. Time to steady-state is approximated at 2–3 weeks without appropriate loading [105]. AUC appears to increase only slightly in proportion to the dose, which is suggestive of linear kinetics up to doses of 600 mg/day and exhibits low inter-patient variability in serum concentrations [106]. Trough concentrations have been shown to correlate with AUCs and represent a suitable measure of exposure [107].

Drug–drug interactions

Isavuconazole undergoes hepatic metabolism involving CYP3A4, CYP3A5, and subsequently UGT and is a moderate CYP 3A4 inhibitor thus drug interactions must be considered.

Isavuconazole therapeutic drug monitoring

TDM is often not pursued for isavuconazole due to its dose-proportional PK, modest interpatient variability and lack of clear efficacy or toxicity thresholds [108]. Less than 3% of patients from the SECURE trial had an average concentration outside a range of 1–7 mg/L, indicating that the recommended clinical dose resulted in serum concentrations that were largely consistent and predictable [109••]. Similar concentration distributions were seen in other trials with > 85–90% of patients having concentrations > 1 mg/L [108, 110]. Thus, regular dosing of isavuconazole results in the achievement of concentrations and exposures that meet PD targets for therapeutic efficacy.

However, two studies have highlighted the need for TDM to monitor sub-therapeutic concentrations in those undergoing renal replacement therapy, on extracorporeal membrane oxygenation circuits and in patients with high BMI [111, 112••]. A case report identified that poor absorption attributable to gastrointestinal graft versus host disease can also interfere with serum concentration [113]. There is an additional role in conducting TDM for infections within drug sanctuary sites such as CNS disease where concentrations are consistently lower than serum concentrations [98, 105, 114]. Co-administration of agents such as rifampicin and flucloxacillin can lead to drug–drug interactions. TDM may be required in this scenario. Evaluation of the impact of pharmacogenomics on isavuconazole PK is also required [115, 116].

Evidence of an exposure–toxicity relationship is evolving. A retrospective evaluation of 19 patients identified that 16% required discontinuation of isavuconazole due to adverse events, with concentrations > 5 mg/L correlating to toxicity [117]. Another study of 45 patients supported the target upper limit for toxicity of 5 mg/L [118]. Results from the post-hoc analysis of the SECURE trial and other studies found an inconsistent relationship between toxicity and serum concentrations [109••, 112••].

TDM for isavuconazole may be less critical compared with other triazole antifungal agents. Further studies are required to identify a clear benefit for TDM with isavuconazole.

Future challenges

Triazole TDM is useful in establishing therapeutic exposure. However, further studies are required to establish the role of TDM on reduction in emergence of resistance, improved cure of infection within a sanctuary sites and treatment of infections with biofilms (bone and joint infections and endovascular infections [4••, 10•].

An important limitation to the universal access of triazole TDM is the high cost and personnel intensive infrastructure required. With the exception of itraconazole, all other triazole monitoring needs the availability of mass spectrometry. Mass spectrometry machines have high acquisition and maintenance costs and are usually available in central laboratories. These assays are not performed daily in most instances due to competing priorities limiting the turn-around time of results. The availability of and access to in-house assays can shorten time to achieving target concentrations and subsequently may contribute to improved outcomes [119]. Future research should focus on development of integrated assays capable of testing multiple assays, immuno-assays, and the use of alternate and accessible matrices such as dried blood spots (DBS) [26, 119]. DBS for TDM addresses the issue of sample acquisition, particularly in the outpatient setting. In DBS sampling, blood is obtained using a finger prick allowing samples to be self-collected. DBS analysis has additional advantages of a smaller sampling volume, simple storage, and transfer of samples at room temperature without biohazard risks during shipment [26]. This technique shows excellent patient satisfaction and allows TDM to be extended to hospitals without a bioanalytical infrastructure and to patients at home [26].

Development of effective algorithms and model-informed precision dosing (MIPD) software to enable precise dosing will help streamline the TDM process, increment its utility, allow individualised prescribing, and enhance physician access to TDM. MIPD uses a population PK model and patient covariates to select anti-infective drug doses and has shown promise in optimising fluconazole exposures in the critically ill population [120]. Robust trials evaluating the utility of MIPD are lacking and are critically needed to prior to its incorporation into clinical practice [120, 121].

There is also a need for the development and evaluation of biomarkers with a prognostic value that can be used to follow disease course and hence inform clinical decisions alongside TDM. Serum galactomannan, 1,3 β-D- glucan and cryptococcal antigen for instance already have correlations with clinical outcomes and may be used to monitor therapeutic progress [122, 123]. Combining a clinical biomarker with concomitant TDM will allow early detection of treatment failure, emerging resistance or highlight instances for dosing escalation or changes in the regimen.

Conclusions

Triazoles are a key part of the armamentarium available in the treatment of IFD. In the current era of rising antifungal resistance, TDM-guided triazole dose optimisation is of particular benefit when susceptibility to antifungals is dose dependent. Utility of routine TDM for voriconazole, posaconazole and itraconazole in the treatment of IFD is well established. Further study is needed to establish the role of triazole TDM in antifungal prophylaxis. Prospective studies evaluating cost-effectiveness of triazole TDM as well as its utility in the context of other triazoles such as isavuconazole and fluconazole are needed. Triazole TDM plays an important role in dose optimisation and individualisation to achieve therapeutic exposure in vulnerable patients with serious IFD at-risk of poor clinical and toxicological outcomes.

Declarations

Conflicts of Interest None.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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