Posaconazole Exposure-Response Relationship: Evaluating the Utility of Therapeutic Drug Monitoring

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Posaconazole has become an important part of the antifungal armamentarium in the prophylaxis and salvage treatment of invasive fungal infections (IFIs). Structurally related to itraconazole, posaconazole displays low oral bioavailability due to poor solubility, with significant drug interactions and gastrointestinal disease also contributing to the generally low posaconazole plasma concentrations observed in patients. While therapeutic drug monitoring (TDM) of plasma concentrations is widely accepted for other triazole antifungal agents such as voriconazole, the utility of TDM for posaconazole is controversial due to debate over the relationship between posaconazole exposure in plasma and clinical response to therapy. This review examines the available evidence for a relationship between plasma concentration and clinical efficacy for posaconazole, as well as evaluating the utility of TDM and providing provisional target concentrations for posaconazole therapy. Increasing evidence supports an exposure-response relationship for plasma posaconazole concentrations for prophylaxis and treatment of IFIs; a clear relationship has not been identified between posaconazole concentration and toxicity. Intracellular and intrapulmonary concentrations have been studied for posaconazole but have not been correlated to clinical outcomes. In view of the high mortality and cost associated with the treatment of IFIs, increasing evidence of an exposure-response relationship for posaconazole efficacy in the prevention and treatment of IFIs, and the common finding of low posaconazole concentrations in patients, TDM for posaconazole is likely to be of significant clinical utility. In patients with subtherapeutic posaconazole concentrations, increased dose frequency, administration with high-fat meals, and withdrawal of interacting medications from therapy are useful strategies to improve systemic absorption.

The triazole antifungal posaconazole has established an important clinical role in the prophylaxis and treatment of invasive fungal infections (IFI) since its approval in Europe and the United States in 2005 and 2006, respectively (17, 64). Posaconazole has demonstrated activity against a broad range of established and emerging fungal pathogens, including *Candida* spp. and *Aspergillus* spp., as well as several endemic fungi and some *Zygomycetes* species (51, 61).

The drug is indicated for prophylaxis of invasive fungal infections in immunocompromised patients and in the treatment of oropharyngeal candidiasis in both the United States and Europe and has also been approved by the European Medicines Agency for the treatment of specified invasive fungal infections (aspergillosis, fusariosis, chromoblastomycosis, and coccidioidomycosis) in patients who are refractory to or intolerant of conventional antifungal therapy (19). Posaconazole is available only as an oral suspension; however, an intravenous formulation and oral tablet with improved bioavailability are reportedly under development (37, 38, 56).

While exposure-response (E-R) relationships and the clinical utility of therapeutic drug monitoring (TDM) have been well defined for other triazole antifungal agents such as itraconazole and voriconazole (2), defining this exposure-response relationship and the value of TDM for posaconazole has remained controversial (10, 31, 66). In the context of prophylactic use of posaconazole, the low numbers of patients developing fungal infection have contributed to the statistical noise surrounding the exposure-response relationship for posaconazole (10), although a relationship between posaconazole concentration and prophylactic efficacy is noted in the prescribing information supplied with the agent in

the United States (48). Given the substantial cost of treatment (67) and high mortality rate of IFIs (45), the application of TDM should be given careful consideration.

This article reviews the available evidence for a relationship between plasma concentration and clinical efficacy for posaconazole, as well as evaluating the utility of TDM and target concentrations for posaconazole therapy.

POSACONAZOLE PHARMACOKINETICS: A NEED FOR TDM

Therapeutic drug monitoring plays an important role in the management of a number of clinically important medications, including antifungal agents other than posaconazole such as voriconazole and flucytosine (2, 24). Indications for the use of TDM typically include improving or ensuring clinical response to therapy by individualizing dose regimens, preventing or investigating drug-related toxicity, and as an aid to establish patient adherence to prescribed medicines. TDM is especially useful when medicines are used for prevention of a clinically important event (such as an invasive and life-threatening fungal infection), and surrogate endpoints to guide pharmacotherapy decision making are not available. Posaconazole exhibits a number of pharmacokinetic characteristics that may justify monitoring of plasma concentrations.

Posaconazole is structurally related to itraconazole and has

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some similarities in its pharmacokinetic behavior, including high plasma protein binding, extensive distribution (with an apparent volume of distribution of 7 to 25 liters/kg), and a prolonged elimination half-life of 15 to 35 h (43). Posaconazole is primarily excreted unchanged in the feces and to a lesser extent in urine, although 20% to 30% appears to be metabolized by hepatic UDP-glucuronosyltransferases (UGT1A4) (23, 46); the drug is also a substrate for P-glycoprotein (43). Studies in healthy volunteers have demonstrated a substantial interpatient variability in posaconazole exposure of between 35% and 50%, while studies in patients have reported a far greater degree of pharmacokinetic variability (71% to 86%) (18). Furthermore, posaconazole exposure in healthy volunteer studies has been found to be approximately 3-fold higher than in patients administered the same dose (18), highlighting the substantial interpatient variability in posaconazole exposure and supporting the need for TDM for dose individualization to ensure that adequate concentrations are achieved to prevent or treat fungal infection.

Absorption of posaconazole after oral administration as a suspension is recognized to be saturable, with multiple divided doses given twice or four times daily increasing systemic exposure by 98% and 220%, respectively, compared to a single once-daily dose of 800 mg (20), with no further absorption observed above this dose (11). Posaconazole oral bioavailability has been estimated at between 8% and 47% (46) and is limited by poor solubility (13, 27, 65). Bioavailability is greatly increased by the coadministration of food (39) or nutritional supplements (35), with higher-fat-content meals further increasing absorption (39). Both the unpredictable relationship between dose and plasma concentration and the large and variable effect of food intake on the bioavailability of posaconazole support the need for TDM.

Furthermore, posaconazole absorption is particularly susceptible to changes that may occur within the gastrointestinal tract related to motility or injury, with diarrhea (33, 34), mucositis (42), and acute graft-versus-host disease (36) having been shown to significantly decrease systemic exposure. Other factors which may significantly affect posaconazole pharmacokinetics include increasing age, which has been associated with higher posaconazole concentrations (58) due to a reduction in the apparent volume of distribution (33), as well as administration via nasogastric tube (15, 58) and hepatic dysfunction (as measured by γ -glutamyl transferase activity ≥ 2 times the upper limit of normal) (34).

Posaconazole is susceptible to a number of clinically significant drug interactions, which have been comprehensively reviewed elsewhere (43). Proton pump inhibitors have been shown to decrease posaconazole exposure by an average of 32% (39) due to increased gastric pH (58); however, some patient studies have found a potentially larger effect on posaconazole bioavailability (52). This interaction is especially problematic due to the high incidence of gastroesophageal reflux in certain patient populations where posaconazole is indicated, such as lung transplant recipients (28). Agents that increase gastrointestinal motility, such as metoclopramide, have also been shown to reduce posaconazole concentrations after concomitant oral administration (39), as have inducers of UDP-glucuronosyltransferases such as rifabutin (40) and phenytoin (41), although the exact mechanism of these interactions is not known.

It is likely that many of these factors contribute to the significant frequency of low posaconazole concentrations noted in some reports. A recent retrospective analysis of posaconazole concen-

tration measurements noted a high incidence of low concentrations, with 33/202 (16.3%) samples having an undetectable posaconazole concentration and 142/202 (70.3%) having posaconazole concentrations < 700 ng/ml (60).

PK/PD RELATIONSHIPS

In vitro studies and animal models have been used to investigate the pharmacokinetic/pharmacodynamic (PK/PD) indices most closely associated with posaconazole efficacy, including the time above the MIC ($T > MIC$) for the fungal pathogen, the maximum concentration of drug in serum over the MIC (C_{max}/MIC), and the area under the concentration-time curve over 24 h divided by the MIC (AUC/MIC ratio). In agreement with findings from a study of other azole antifungals (59), the AUC/MIC ratio is the PK/PD index that is most predictive of posaconazole efficacy for yeasts (1); studies performed with molds have identified both the $T > MIC$ (26) and the AUC/MIC ratio (30, 47) as important PK/PD indices. These findings demonstrate a significant exposure-response relationship for posaconazole efficacy in the context of *in vitro* and animal models.

Posaconazole is known to exhibit protein binding of 98% to 99% in serum (1, 12). As it is normally accepted that only the unbound fraction of a drug in serum is pharmacologically active, the low posaconazole concentrations achieved in many patients would suggest that unbound posaconazole concentrations are often below the median MICs for many fungal pathogens when the degree of protein binding is considered (44). This would be expected to lead to inadequate antifungal efficacy and treatment failure, which is inconsistent with the high level of clinical efficacy observed in posaconazole clinical trials. A recent study by Lignell and colleagues demonstrated a significant antifungal effect of posaconazole against *Candida* isolates at unbound posaconazole concentrations of only 10% of the known fungal MIC in serum; this effect was not seen in protein-free media (44). Those authors suggest that a flux of protein-bound posaconazole to its fungal binding target might explain the observed pharmacodynamic effect.

PLASMA EXPOSURE-RESPONSE RELATIONSHIP

IFI prophylaxis. A number of clinical studies of posaconazole efficacy have included a pharmacokinetic component, facilitating the assessment of a relationship between posaconazole plasma concentrations and clinical efficacy (Table 1). Among studies assessing posaconazole for prophylaxis against fungal infections, a study combining the results of two pivotal efficacy trials (9, 63) provided the strongest evidence for an exposure-response (E-R) relationship for efficacy (31). In that analysis, patients were stratified by clinical failure rate according to the quartile posaconazole average steady-state concentration (C_{avg}); lower clinical failure rates were associated with higher C_{avg} quartiles in both trials (31). Those authors proposed a target C_{avg} of 700 ng/ml for posaconazole prophylaxis, as no additional reduction in clinical failure rate was seen above this concentration (31). In those clinical trials, the median posaconazole C_{avg} values were 915 ng/ml (range, 22 to 3,650 ng/ml) among 252 hematopoietic stem cell transplant recipients with graft-versus-host disease and 490 ng/ml (range, 90 to 2,200 ng/ml) in 215 neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes (31).

The results of the analysis by Jang et al. (31) have been disputed

TABLE 1 Published studies including an analysis of an exposure-response relationship for posaconazole efficacy^a

Reference	Indication for posaconazole	Study population	No. of patients ^b	Posaconazole dosage	Plasma exposure-response relationship	Recommended target threshold
Jang et al. (31)						
Data from Ullmann et al. (63)	Prophylaxis	HSCT recipients also taking immunosuppressants for GVHD	252	200 mg three times daily	Yes; clinical failure reduced with increasing C_{avg} quartiles (C_{avg} range, 22–3,650 ng/ml)	$C_{avg} > 700$ ng/ml (prophylaxis)
Data from Cornely et al. (9)	Prophylaxis	Patients with neutropenia due to chemotherapy for AML or MDS	215	200 mg three times daily	Yes; clinical failure reduced with increasing C_{avg} quartiles (C_{avg} range, 90–2,200 ng/ml)	$C_{avg} > 700$ ng/ml (prophylaxis)
Eiden et al. (16)	Prophylaxis	Patients with primarily hematological malignancies	63	200 mg three times daily	Yes; 1 patient developed probable IFI with a concn of 110 ng/ml, compared to overall median day 7 concn of 440 ng/ml	Not stated
Lebeaux et al. (42)	Prophylaxis/treatment	Various; primarily patients with hematological malignancies (69%)	54 (36 prophylaxis, 18 treatment)	Prophylaxis, 200 mg three times daily; treatment, 400 mg twice daily	Prophylaxis: yes; 2 patients with clinical failure had concn of 310 and 190 ng/ml vs median concn of 630 ng/ml Treatment: unclear; 2 of 4 patients with treatment failure or stable disease had high concn	>500 ng/ml (prophylaxis) 34 of 54 patients achieved concns above 500 ng/ml
Neubauer et al. (52)	Prophylaxis	Hematology patients	27	Initial dose 200 mg three times daily	No; 2 patients developed possible IFI with C_{min} of 900 ng/ml vs median of 740 ng/ml	N/A
Bryant et al. (3)	Prophylaxis	Patients with hematological malignancies	21	Initial dose 200 mg three times daily	Unclear; 3 patients developed IFI, 1 due to drug-resistant <i>C. glabrata</i> ; C_{avg} of other 2 patients, 190 ng/ml and 410 ng/ml compared to mean C_{avg} of 360 ng/ml	Not stated
Shields et al. (58)	Prophylaxis/treatment	Cardiothoracic transplant recipients	17 (11 prophylaxis, 6 treatment)	Variable; most common initial dose, 200 mg three times daily	Yes; median C_{min} of 1,550 ng/ml in patients with therapeutic success vs 340 ng/ml in patients with therapeutic failure (combined prophylaxis and treatment)	$C_{min} > 500$ ng/ml (prophylaxis/treatment) 9 of 17 patients achieved concns above 500 ng/ml
Walsh et al. (66)	Treatment (salvage)	Patients with IA refractory to or intolerant of conventional therapy	67	200 mg four times daily (inpatient), 400 mg twice daily (outpatient)	Yes; proportion of clinical responders increased with increasing C_{avg} quartile (mean C_{avg} range, 134–1,250 ng/ml)	C_{avg} of 1,250 ng/ml associated with highest response (salvage treatment)
Ullmann et al. (62)	Treatment	Patients with persistent febrile neutropenia or refractory IFI	74 ^c	Multiple dose regimens; see reference	N/A; dose regimen compared with response rather than plasma concn	N/A

(Continued on following page)

TABLE 1 (Continued)

Reference	Indication for posaconazole	Study population	No. of patients ^b	Posaconazole dosage	Plasma exposure-response relationship	Recommended target threshold
Felton et al. (22)	Treatment	Patients with chronic pulmonary aspergillosis	66	Initial dose, 400 mg twice daily	No; initial concn did not impact response	N/A
Catanzaro et al. (5)	Treatment	Patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis	20	400 mg daily ^d (capsule form)	No; no correlation between C_{avg} and treatment failure (data not presented)	N/A

^a HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; IA, invasive aspergillosis; IFI, invasive fungal infection; N/A, not applicable; C_{avg} , average steady-state plasma concentration; C_{min} , trough plasma concentration.

^b Data represent numbers of patients with available posaconazole concentration data.

^c Efficacy-evaluable patients.

^d Two patients received 800 mg daily for 16 and 17 days.

because of concerns with regard to the composite definition of clinical failure used in the analysis and the discrepancy between that more liberal endpoint and the lower number of patients who developed proven or probable invasive fungal disease as a result of failing posaconazole therapy in those trials (10). However, other studies supporting an E-R relationship for posaconazole prophylaxis have also been published (16, 42, 58).

Lebeaux et al. undertook a retrospective review of 54 patients with primarily hematological malignancies who had a posaconazole concentration measured after at least 5 days of therapy, with 36 patients taking posaconazole for antifungal prophylaxis (42). While only two patients failed posaconazole prophylaxis, those patients had posaconazole concentrations of 310 and 190 ng/ml, compared to a median concentration of 630 ng/ml in patients who achieved optimal clinical outcomes (42), supporting a possible E-R relationship for posaconazole efficacy.

A study conducted in cardiothoracic transplant recipients has also provided evidence of an E-R relationship for efficacy for posaconazole. Shields et al. found a higher median trough concentration (C_{min}) in patients with therapeutic success than in those who failed posaconazole and also found that transplant recipients with a posaconazole C_{min} consistently >500 ng/ml were more likely to have a successful clinical outcome (58). Notably, that study combined the results of patients receiving posaconazole for prophylaxis as well as for treatment of IFIs, suggesting a target concentration of >500 ng/ml for both indications (58).

Eiden and colleagues carried out a prospective study of posaconazole therapeutic drug monitoring in 63 hematology patients (16). While only a single patient developed a probable IFI in that study, the posaconazole concentration in that patient preceding treatment failure (day 7; 110 ng/ml) was far lower than the median posaconazole concentration observed in the study at the same time after the start of posaconazole therapy (day 7; 440 ng/ml) (16).

While the studies described above have provided evidence to support an E-R relationship for the efficacy of posaconazole prophylaxis, one study in hematology patients found that two patients who developed possible IFIs while taking posaconazole prophylaxis had concentrations of 900 ng/ml compared with a median concentration of 740 ng/ml in that study (52). A study by Bryant et al. in 21 neutropenic patients with hematological malignancies found three patients with breakthrough IFI, with one case attributed to a posaconazole-resistant *Candida glabrata* infection

(3). In the two other patients failing therapy in that study, breakthrough infections were classified as possible IFIs, with average steady-state posaconazole concentrations of 190 and 410 ng/ml, compared to an overall mean concentration of 360 ng/ml (3). These findings demonstrate that ensuring that sufficient posaconazole concentrations are achieved may not always lead to positive clinical outcomes, although further interpretation of clinical failure in these studies is difficult, as four of five IFIs detected only met the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria (14) for possible IFI.

Treatment of IFI. Several studies have also analyzed an E-R relationship for posaconazole in the treatment of IFI. Walsh and colleagues investigated the treatment of invasive aspergillosis with posaconazole in patients refractory to or intolerant of conventional antifungal therapy, with plasma concentrations available for 67 of the 107 posaconazole-treated patients (66). When patients were stratified into quartiles based on C_{avg} , clinical response was seen to improve with increasing C_{avg} quartiles (66). A mean C_{avg} concentration of 1,250 ng/ml in the uppermost quartile was associated with the highest clinical response of 75% (66).

In other studies evaluating posaconazole for the treatment of fungal infections, E-R analyses have often been limited by low sample size and have produced conflicting results. In a study of 20 patients with chronic pulmonary or nonmeningeal disseminated coccidioidomycosis, the authors found a mean posaconazole plasma concentration of 1,284 ng/ml and concluded that no correlation could be drawn between plasma concentration and clinical failure (5). Felton et al. investigated patients treated with posaconazole for chronic pulmonary aspergillosis, finding a median posaconazole plasma concentration of 1,280 ng/ml (22). The initial posaconazole concentration did not significantly affect treatment outcome at 6 or 12 months in that study, although later posaconazole concentrations were not assessed (22). While neither of those studies found an association between posaconazole concentration and response to therapy, both studies reported a high median posaconazole concentration, which may have reduced the ability to observe an E-R relationship, as most patients achieved high systemic exposure of the drug.

Exposure-response relationship for toxicity. Fewer studies have investigated an E-R relationship regarding posaconazole toxicity. Using data pooled from two patient studies of posaconazole

($n = 467$ patients), Jang and colleagues found that the incidence of a number of treatment-related adverse events was lower in patients with lower posaconazole plasma concentrations when patients were stratified by quartile posaconazole concentration, suggesting a possible E-R relationship for posaconazole safety; however, those differences did not reach statistical significance (31). A study by Moton et al. pooled posaconazole safety data from 18 studies in healthy volunteers and two subsets from other trials with posaconazole doses ranging from 50 to 1,200 mg/day, finding no relationship between adverse events and dose (49). Smaller studies have not observed a correlation between posaconazole concentration and adverse events (5). Based on those studies, a clear relationship between posaconazole safety and exposure seems unlikely.

Confounding factors and PK/PD indices. A number of studies have provided evidence of an E-R relationship between posaconazole concentration and clinical outcome, for both prevention and treatment of IFIs (16, 31, 42, 58, 66). However, not all studies identified an E-R relationship for posaconazole efficacy, and a number of limitations are apparent for many of the studies that have assessed posaconazole E-R relationships.

Small sample size is a significant issue for most available studies assessing posaconazole TDM and E-R relationships. This is particularly apparent for investigations of the use of posaconazole for IFI prophylaxis, where the number of patients who develop breakthrough fungal infection has generally been low, with the exception of one larger study (31). The lack of fungal MIC testing in most studies may potentially confound the assessment of E-R relationships, and epidemiological variations in fungal pathogens (53) may contribute to differences between studies with respect to the risk of breakthrough IFI or of IFI treatment failure.

The application of AUC/MIC ratio targets derived from animal models to posaconazole therapy in patients remains an important area for future research, particularly for examining the role of protein binding. Compared to unbound AUC/MIC ratios associated with efficacy in animal models (1), unbound posaconazole concentrations achieved in patients are often significantly lower.

In a cohort of neutropenic stem cell transplant recipients receiving posaconazole at 200 mg four times daily, the AUC from 0 to 24 h (AUC_{0-24}) averaged 8.7 mg · h/liter (27). Assuming posaconazole protein binding of 98% and an MIC for *Candida* spp. of 0.063 mg/liter (55), an unbound AUC/MIC ratio of 2.8 was achieved. This ratio is severalfold lower than the posaconazole unbound AUC/MIC ratio of 16.9 associated with a 50% maximal effect in a murine model of disseminated candidiasis (1). The recent finding of antifungal activity in the presence of posaconazole at unbound concentrations far below the fungal antibiotic MIC may account for this apparent discrepancy between AUC/MIC ratio targets determined in animal models and concentrations associated with clinical success in patient studies (44).

IS PLASMA THE BEST SAMPLE MATRIX FOR POSACONAZOLE TDM?

Current practice in posaconazole TDM involves measurement of plasma concentrations, for which a number of assays have been reported (6, 25, 32, 50, 57). The appropriateness of plasma concentrations of posaconazole as a correlate of drug response has been disputed in the literature, with intrapulmonary or intracellular concentrations suggested as being of potential interest (4, 10). A study by Conte et al. investigated the intrapulmonary and

plasma pharmacokinetics of posaconazole in healthy volunteers at the steady state, measuring posaconazole concentrations in pulmonary epithelial lining fluid (ELF) and alveolar cells (AC) following bronchoscopy (8). While ELF concentrations of posaconazole were similar to plasma concentrations (ELF/plasma AUC_{0-12} steady-state [$AUC_{0-12,ss}$] ratio of 0.84), concentrations in AC were significantly higher (AC/plasma $AUC_{0-12,ss}$ ratio of 33) (8). A later study with a similar design in lung transplant recipients found lower posaconazole concentrations across all compartments and a similar ELF/plasma AUC ratio but found a higher AC/plasma AUC ratio of 48 (7). Those researchers suggested that the high AC concentrations of posaconazole may be clinically important due to the role of alveolar macrophages in the early stages of infection with *Aspergillus* spp. (7); however, the invasiveness and expense of a bronchoscopy compared with plasma sampling greatly diminishes the viability of routine measurement of posaconazole concentrations in alveolar cells or ELF. Further study of the predictive value of the ELF/plasma ratio may increase the clinical relevance of this metric for posaconazole therapy.

Farowski and colleagues assessed the intracellular concentrations of posaconazole in peripheral blood mononuclear cells (PBMCs), polymorphonuclear leukocytes (PMNs), and red blood cells (RBCs) in patients receiving posaconazole for prophylaxis of fungal infections (21). Mean posaconazole concentrations were found to be far higher in PBMCs and PMNs compared to plasma (intracellular-to-extracellular concentration ratios of 22.5 and 7.66, respectively), whereas concentrations in RBCs were approximately 10% of those observed in plasma (21). More recently, an *in vitro* study in epithelial cells demonstrated fungistatic activity with intracellular posaconazole when extracellular drug was removed (4). However, no study has yet investigated a relationship between intracellular posaconazole concentrations and clinical response to therapy. In addition to the increased complexity involved in measuring intracellular concentrations, the far greater evidence of an E-R relationship between plasma posaconazole concentrations and clinical efficacy (Table 1) suggests plasma monitoring should remain the sample matrix of choice for TDM of posaconazole.

IMPLICATIONS FOR CLINICAL PRACTICE

Posaconazole is an important therapy in the antifungal armamentarium. While its challenging pharmacokinetic properties and wide interpatient variability suggest the need for TDM, until recently the dearth of information regarding a relationship between exposure and response has hindered the case for monitoring posaconazole plasma concentrations, as an E-R relationship is crucial to the clinical utility of TDM for dose individualization. In light of the poor prognosis and high cost of treating IFIs (45, 67), substantial evidence of an E-R relationship for efficacy for both prophylaxis and treatment of fungal infections, and the common finding of low posaconazole plasma concentrations (3, 16, 54), arguments supporting the value of TDM for posaconazole are compelling (Table 2).

Timing of concentration monitoring in relation to dose is crucial to the accuracy and utility of TDM for all medications. Studies assessing E-R or TDM for posaconazole have used a variety of times for plasma sampling, including the average steady-state concentration (C_{avg}) (5, 31, 66) and the trough concentration (C_{min}) (52, 58), as well as utilizing the first concentration sample, irrespective of timing (22, 42). These differences complicate a rec-

TABLE 2 Advantages and limitations for therapeutic drug monitoring of posaconazole

Parameter	Advantage of TDM	Limitation of TDM
Evidence of an exposure-response relationship for posaconazole efficacy	✓	
Saturable absorption	✓	
Nonlinear and variable relationship between dose and plasma concn	✓	
High interpatient variability in pharmacokinetics	✓	
Significant drug-drug interactions	✓	
Large food effect	✓	
Validated assays available	✓	
No evidence of an exposure-response relationship for posaconazole safety		✓
Target plasma concns uncertain		✓

ommendation of sampling time; however, due to the frequent dosing of posaconazole compared with its extended terminal half-life, plasma concentration-time profiles are often relatively flat after multiple doses (11). While this may justify the use of “untimed” concentrations, until recently this assumption had not been investigated. In a cohort of patients with hematological malignancies receiving posaconazole at 400 mg twice daily, Heinz et al. compared mean posaconazole concentrations timed at a trough, 4 h postdose, and 8 h postdose (29). Mean concentrations were found to be 645, 678, and 616 ng/ml, respectively, with the majority of patient trough and 4-h posaconazole concentrations differing by <20% (29). Although the use of trough posaconazole concentrations is preferable to ensure that adequate exposure is maintained, those findings indicate that concentrations measured earlier in the dosing interval may still be useful for posaconazole TDM.

Defining accurate target concentrations for posaconazole therapy remains challenging. For use of posaconazole as fungal prophylaxis, a target trough concentration of >500 ng/ml has previously been recommended (2) and has been supported by several authors (42, 58); however, a larger study identified a number of breakthrough fungal infections in patients with posaconazole concentrations between 500 and 700 ng/ml (31). While the results of those studies suggest that patients treated at posaconazole concentrations between 500 and 700 ng/ml may be at a lower risk of breakthrough IFI than at concentrations below 500 ng/ml, considering the apparent lack of concentration-dependent adverse events, a target trough posaconazole concentration of >700 ng/ml as suggested by Jang et al. (31) is now preferable to minimize the risk of breakthrough IFIs (Table 3). For cases in which posaconazole is used for the treatment of refractory IFIs, far less informa-

tion is available to guide therapy. A provisional target trough concentration of >700 ng/ml is suggested, with escalation to >1,250 ng/ml if response is poor, based on the results of Walsh et al. (66); however, achieving this level of exposure may be difficult in many patients.

As posaconazole takes between 7 and 10 days to achieve steady state (11, 61), concentrations should ideally be measured >7 days after starting therapy. For patients with subtherapeutic posaconazole concentrations, pharmacokinetic studies indicate that increasing the dose frequency is most effective in increasing posaconazole exposure; in healthy volunteers taking posaconazole at 400 mg every 12 h, dividing this dose into 200 mg taken every 6 h has been shown to significantly increase systemic exposure (20). As no further increase in systemic exposure has been observed with cumulative daily doses above 800 mg (11, 62), increasing the posaconazole dose above this level is unlikely to improve exposure. Additional strategies to improve the systemic absorption include administration with a high-fat meal or with a nutritional supplement (35, 39), as well as withdrawing interacting medications (particularly proton pump inhibitors) where possible. While the clinical importance of monitoring plasma concentrations for posaconazole is clear, further investigation of the E-R relationship, particularly for the treatment of IFI, is needed to further refine the target concentrations most closely associated with optimal efficacy.

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TABLE 3 Provisional target plasma concentrations for posaconazole

Posaconazole indication	Target trough concn (ng/ml)
IFI ^a prophylaxis	>700
Treatment of IFI	>700
	Increase to >1,250 if response is poor

^a IFI, invasive fungal infection.

- multiple doses in healthy adults. *Antimicrob. Agents Chemother.* 47: 2788–2795.
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