Antifungal serum concentration monitoring: an update

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Invasive fungal infections (IFIs) are occurring with increasing incidence and are associated with significant morbidity and mortality. Understanding the relationship between the pharmacokinetic and pharmacodynamic properties of antifungals is essential to optimize the potential for favourable clinical and microbiological outcomes while minimizing risks of treatment-related toxicity. Antifungal serum concentrations may aid in the determination of appropriate dosing in select circumstances. The polyene and echinocandin classes of antifungals lack sufficient data to justify serum concentration monitoring in routine clinical practice. In contrast, serum concentration monitoring of fluconazole may help to reduce the risk of treatment-related haematological toxicity. Determination of itraconazole serum concentrations is advised in situations where the drug is used for prolonged periods to treat serious IFIs (such as invasive aspergillosis or histoplasmosis) because of variability in absorption following oral administration (most notable for the capsule formulation). The use of serum concentration monitoring during therapy with the extended-spectrum triazoles (i.e. voriconazole and posaconazole) is still evolving, due primarily to inter-patient variability in drug exposure combined with sparse data regarding relationships with efficacy (posaconazole) and both safety and efficacy (voriconazole).

Keywords: pharmacodynamics, pharmacokinetics, azoles

Introduction

The incidence of invasive fungal infections (IFIs) has increased significantly over the past two decades, largely due to an increased number of patients at risk.1–5 In 2004, Candida spp. was identified as the fourth leading cause of nosocomial bloodstream infections.6 While over half of these infections are still due to C. albicans, an increase in non-albicans Candida as a cause of candidemia has been noted in several reports.3,6,7 In contrast to invasive candidiasis, invasive aspergillosis is diagnosed largely in immunocompromised patients.7 In addition, new fungal pathogens causing IFIs are emerging and include non-fumigatus species of Aspergillus, zygomycetes, hyaline moulds, dematiaceous fungi and opportunistic yeast-like fungi.1

While treatment outcomes vary with both pathogen and underlying patient population, they are generally less than optimal.5,8–10 In a study of over 5000 haematopoietic stem cell transplant recipients, the 1 year survival rate after the diagnosis of an invasive mould infection was <20%.5 Crude mortality rates observed in patients with invasive candidal infections generally range between 20% and 50%.11–13 In solid organ transplant patients with zygomycetes, overall mortality was 49%, while rhinocerebral disease was associated with 93% mortality.14

As reduction or elimination of risk factors for IFIs is often problematic during treatment, it is important to ensure appropriate antifungal therapy in order to optimize the potential for a favourable patient outcome while minimizing the risks of treatment-related toxicity. This is especially important as delays in the administration of adequate antifungal therapy are associated with increased hospital mortality.11,15,16 Numerous strategies have been proposed in attempts to either prevent IFIs or to optimize treatment outcomes for IFIs. Such strategies include (but are not limited to) use of prophylaxis in high-risk patients, combination antifungal therapy, use of immunostimulants, use of newer antifungal agents and pre-emptive antifungal therapy.17 In addition to antifungal drug selection, determination and administration of the optimal dose and frequency are essential.18 In general, this requires integration of knowledge regarding the drug’s pharmacokinetic profile (absorption, metabolism, distribution and elimination) with its antymycotic properties.19

Established relationships between drug exposure and either efficacy or safety provide an opportunity to objectively determine the optimal dose. For most antibiotics (including antifungals), the activity of the agent is related to one or more of the following: (i) time that the serum concentration exceeds the MIC of the organism (t > MIC); (ii) maximum serum concentration (Cmax) to MIC ratio (Cmax/MIC); and/or (iii) the area under the serum concentration–time curve (AUC) in relation to MIC (AUC/MIC).20,21 Determination of such relationships for antifungals used to treat serious IFIs in humans, however, may

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be problematic due to the great dependency on co-morbidities and immune function of the host. Although concentrations in various tissues and body fluids are of greatest interest (especially at the site of infection or target organ for toxicity), serum drug concentrations have generally served as a reasonable surrogate.\(^2^3\) In contrast, serum drug concentration monitoring would not be clinically useful in situations when such relationships have not been established, for whom exposure can be accurately predicted in the absence of such data (such as from dosing information and estimates of organ function) and/or for which a validated assay is not readily available to provide results in a timely fashion.

In contrast to the standard practice of serum concentration monitoring of select antibacterials (most notably vancomycin and the aminoglycosides), the practice of serum drug concentration monitoring for antifungal agents is in its infancy. However, the recent introduction of newer agents for the prevention and treatment of IFIs, the need to optimize antifungal selection and dose, and the advances in knowledge regarding pharmacokinetic and pharmacodynamic properties of various antifungals, make it necessary to update this topic. The objective of this review is to summarize recent data regarding the potential utility of serum drug concentration monitoring for antifungals used to treat IFIs. When appropriate, recommendations regarding therapeutic drug monitoring are described; they are presented in Table 1.

### Table 1. Summary of data supporting the application of serum concentration monitoring for newer antifungal agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Serum concentration monitoring recommended</th>
<th>Peak</th>
<th>Trough</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>no</td>
<td>n/a</td>
<td>n/a</td>
<td>toxicity seen with 2 h post-dose concentrations &gt;100 mg/L</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>yes</td>
<td>2 h post-dose: 30–80 mg/L for cryptococcal infections; 40–60 mg/L for candidal meningitis</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>no</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>yes</td>
<td>n/a</td>
<td>&gt;0.5 to 1 mg/L</td>
<td>to ensure adequate absorption</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>yes(^a)</td>
<td>&lt;6 mg/L</td>
<td>&gt;2 mg/L</td>
<td>to ensure efficacy, limit toxicity</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>yes(^a)</td>
<td>&gt;1.48 mg/L(^b)</td>
<td>n/a</td>
<td>limited data, average concentration of 1.25 mg/L associated with 75% response(^b)</td>
</tr>
<tr>
<td>Caspofungin, micafungin and anidulafungin</td>
<td>no</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Consider (when available) in ‘non-responders’, questionable medication compliance, significant drug–drug interactions, suspected toxicity.

\(^b\)Data based on treatment of Aspergillus with posaconazole.

Amphotericin B has consistently demonstrated concentration-dependent killing and prolonged growth suppression following drug exposure and removal (known as post-antifungal effect) in numerous studies of both yeast and filamentous fungi.\(^2^1,2^3,3^2\) In general, animal models of invasive infection with both Candida and Aspergillus spp. indicate the need for \(C_{max}/MIC\) values between 2 and 4.\(^2^1,3^1,3^2\) Serum and tissue concentrations of amphotericin B, however, vary greatly with formulation (especially among the lipid-based products).\(^3^0\)

Data relating serum concentrations of amphotericin B to either efficacy or toxicity are sparse. In addition, attempts to examine correlations of outcome to MIC have been problematic due (in part) to the narrow MIC ranges tested and the dependency on host factors (rather than pharmacodynamics) for successful outcome. A recent study examining outcomes of a subset of paediatric patients treated with liposomal amphotericin B demonstrated a relationship between improved clinical outcome and a \(C_{max}/MIC\) ratio exceeding 40.\(^3^4\) In this small subset of patients (\(n = 10\)), those achieving a complete response had a significantly higher \(C_{max}/MIC\) ratio (67.9 ± 17.5) than those patients only achieving a partial response (40.2 ± 13.3) (\(P = 0.021\)).

Despite in vitro, animal and limited human data demonstrating relationships between drug exposure and efficacy, the
clinical efficacy or toxicity associated with amphotericin B appears to be related largely to the formulation studied, underlying patient population and/or the causative fungal pathogen and not specific serum concentrations.\textsuperscript{35,36} Therefore, serum concentration monitoring is not routinely performed for the various amphotericin B formulations.

**Flucytosine**

Flucytosine, one of the oldest antifungal medications, is a synthetic compound originally developed for its possible antitumour activity. The clinical use of flucytosine is limited due to its toxicities (gastrointestinal, haematological and neurological), rapid development of resistance (when used as monotherapy) and lack of parenteral formulations.\textsuperscript{37} It is generally utilized in combination with other agents for the treatment of select IFIs, notably cryptococcal meningitis,\textsuperscript{38} severe or refractory candidiasis\textsuperscript{23} or aspergillosis.\textsuperscript{24}

*In vivo* studies, as well as one conducted with a neutropenic murine candidiasis model, demonstrate that the \( t > MIC \) is the pharmacodynamic parameter most closely correlated to outcome with flucytosine monotherapy.\textsuperscript{39,40} In contrast, AUC/MIC best predicted treatment outcome in a non-neutropenic murine model of invasive aspergillosis.\textsuperscript{41}

Monitoring of flucytosine serum concentrations in an attempt to minimize drug-related haematological toxicity is perhaps the most well-established use of such techniques among the antifungals. A retrospective, observational study of 53 intensive care unit patients reported that patients with flucytosine concentrations exceeding 100 mg/L exhibited significantly higher incidence of thrombocytopenia (\( P < 0.05 \)) and elevated liver enzymes (\( P < 0.05 \)) when compared with the total population.\textsuperscript{42} A linear correlation was found between flucytosine clearance and thrombocyte nadir. The incidence of toxicity thought related to flucytosine serum concentrations (myelosuppression or hepatotoxicity) was reported in patients treated with flucytosine (in combination with amphotericin B) for cryptococcal meningitis.\textsuperscript{43} Flucytosine toxicity occurred in 23 of 37 (62\%) patients with serum concentrations exceeding 100 mg/L for 2 or more weeks, compared with only 15 of 48 (31\%) with concentrations \(< 100 \text{ mg/L} (P = 0.005). \) Six of seven patients with hepatotoxicity had serum concentrations \( > 100 \text{ mg/L} \) for 2 or more weeks. However, it was noted that if an elevated concentration only occurred once, it was not a predictor for toxicity. In contrast to toxicity, data in humans are lacking to correlate serum concentrations with efficacy for flucytosine. Despite this, published guidelines for the use of flucytosine (in combination with other antifungals) for the treatment of cryptococcal infections\textsuperscript{25} and meningitis due to *Candida* spp.\textsuperscript{23} recommend maintaining 2 h post-dose concentrations of 30–80 and 40–60 mg/L, respectively.

Based on available data, a 2 h post-dose concentration of flucytosine should be obtained after 3–5 doses have been administered. A reasonable goal is to maintain such concentrations \( > 25 \text{ mg/L} \) while avoiding concentrations exceeding 100 mg/L. Available assays for the measurement of flucytosine include bioassay, gas–liquid chromatography and HPLC.\textsuperscript{44–46} However, these may not be readily available in all institutions. In all instances, adjustments of flucytosine dosing in patients with renal insufficiency, in addition to close monitoring of both renal function and blood counts, would be advised.

**Azoles**

Azole antifungal agents currently used to treat IFIs include fluconazole, itraconazole, voriconazole and posaconazole. All of these agents possess potent activity *in vitro* against a wide variety of pathogens causing IFIs, including a variety of *Candida* spp. and endemic mycoses (i.e. *Histoplasma*, *Blastomyces* and *Coccidioides*).\textsuperscript{47} The expanded-spectrum triazoles (voriconazole and posaconazole) demonstrate increased potency *in vitro* (relative to fluconazole) against non-*albicans Candida* (including *C. glabrata* and *C. krusei*).\textsuperscript{47} With the exception of fluconazole, these agents demonstrate activity *in vitro* against *Aspergillus* spp., with voriconazole considered by many to be the ‘drug-of-choice’ to treat invasive aspergillosis.\textsuperscript{48} Posaconazole has additional activity against *zygomycetes*.\textsuperscript{47} Azole antifungals are used to treat a broad spectrum of IFIs, including invasive candidiasis,\textsuperscript{23} aspergillosis,\textsuperscript{25} cryptococcal disease,\textsuperscript{23} disseminated cases of endemic mycoses,\textsuperscript{26–28} fusariosis\textsuperscript{49} and scedosporiosis.\textsuperscript{30}

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HPLC is the most utilized method. However, such assays are not routinely available. In addition, because of the predictability of fluconazole serum concentrations from dosing and organ function information, current data do not support the routine use of serum concentration monitoring for fluconazole.

*Itraconazole*. Itraconazole, a synthetic triazole antifungal, is available as a capsule, an oral solution and an intravenous solution.63 Both the oral solution and the intravenous solution combine itraconazole with hydroxypropyl-β-cyclodextrin in order to increase the solubility of the compound.63 A significant amount of inter-patient variability in serum concentrations following oral administration of itraconazole has been observed and is most notable with the capsule formulation.64 A retrospective study of steady-state itraconazole trough concentrations in 16 patients receiving 400–600 mg/day orally exhibited up to a 15-fold difference in serum concentrations.65 Absorption of the capsule is pH dependent, requiring an acidic environment. Therefore, it is recommended to be given with a full meal or a cola.65,66 In contrast, absorption of the oral solution is enhanced in the fasted state.67 Peak serum concentration at steady-state following the oral solution (200 mg every 12 h) ranged from 0.513 to 2.278 mg/L, with a median of 1.326 mg/L.68 In comparison, the peak serum concentration at steady-state following the capsule formulation (200 mg every 12 h) ranged from 0.297 to 1.609 mg/L with a median of 0.741 mg/L. As the oral solution has been shown to have enhanced absorption, it is generally the preferred formulation for use.68

There are limited published studies in humans examining correlations between serum concentrations of itraconazole and either prophylactic efficacy or treatment outcome. In 170 neutropenic patients receiving prophylaxis with itraconazole from 1994 to 1998, 20 patients were identified who had developed an IFI.69 Trough itraconazole serum concentrations exceeded 0.5 mg/L (measured by HPLC) in only 48%. In contrast, 100% of the uninfected patients exhibited concentrations exceeding 0.5 mg/L (P = 0.039). Patients who were shown to have fatal infections were also shown to have lower itraconazole concentrations immediately prior to the occurrence of the infection as compared with those with non-fatal infections (0.120 mg/L versus 0.690 mg/L, respectively) (P = 0.039). In another prophylactic study, sustained itraconazole concentrations that were <0.25 mg/L for 2 weeks were associated with a significantly higher incidence of invasive infections when compared with those with concentrations over 0.25 mg/L (66.6% versus 15.8%, P < 0.001).70 However, IFIs were also observed in patients despite concentrations exceeding 0.25 mg/L. In contrast to the previous study, concentrations in this study were drawn at least 2 h after dose administration. In AIDS patients receiving itraconazole (200 mg/day) for the treatment of oropharyngeal candidiasis, those with serum concentrations >0.50 mg/L had success rates ranging from 65% to 89%, whereas those with concentrations ≤0.50 mg/L had a 44% to 88% success rate.54 This analysis, however, did not specify the sampling time of the concentration with regard to dose. Published data regarding relationships between itraconazole serum concentrations and toxicity are even more scant. Adrenal insufficiency was reported in one patient with a serum concentration of >5 mg/L.71

HPLC is the method most commonly utilized, since the bioassay also detects a major metabolite (hydroxy-itraconazole) and therefore yields higher values (~2–10-fold) than the HPLC.72 However, it is not routinely available in most institutions. The optimal concentration for all infections has not been defined. However, the treatment guidelines for histoplasmosis suggest a steady-state random serum concentration target of at least 1 mg/L.29 Serum concentration monitoring is also recommended in the published guidelines when itraconazole is used for the treatment of Aspergillus.24 For the treatment of IFIs requiring prolonged itraconazole therapy, determination of serum concentrations 2–4 h after an oral dose may be performed to document absorption. Overall, a trough concentration of itraconazole measured by HPLC of at least 0.5–1 mg/L should be targeted.

*Voriconazole*. Unlike fluconazole, voriconazole exhibits wide intra- and inter-subject variability in serum concentrations.73,74 In healthy volunteers, oral bioavailability is estimated to be >90%, but may be reduced by more than 20% when administered with food.75,76 Major enzymes involved in voriconazole metabolism include CYP2C9, CYP3A4 and CYP2C19.77 The latter is associated with significant inter-patient variability due to the genetic polymorphism of the enzyme.78 For example, ~15% to 20% of Asian populations and 3% to 5% of Caucasians and African Americans have been shown to be poor metabolizers.79 In patients who are poor metabolizers, voriconazole serum concentrations can be up to four times higher than in other patients, including those considered extensive metabolizers.77 Voriconazole serum concentrations are significantly reduced by many medications including rifampicin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz and rifabutin.76,80 Finally, voriconazole exhibits non-linear kinetics related to its saturable metabolism.76,80 As a result of non-linear kinetics, small changes in dose may effect a disproportionally large change in serum concentration.

High variability of voriconazole serum concentrations has been documented both in normal volunteers and in patients receiving voriconazole for an IFI.80,81 For example, in allogeneic haematopoietic stem cell transplant recipients receiving voriconazole 200 mg orally twice daily (n = 34), the mean (± SD) serum concentration was 2.0 (± 1.8) mg/L.24 In patients receiving 300 mg twice daily (n = 7), average concentrations of 2.5 (± 1.9) mg/L were reported. Serum concentrations appear to have been drawn randomly without regard to the timing of dose administration. Similarly, in a small study of 24 subjects at risk for IFIs, the mean C_{max} after 14 days of therapy was 3.0 and 4.7 mg/L for the 200 and 300 mg twice daily groups, respectively.82 These parameters were associated with inter-subject coefficients of variation of 51% for the 200 mg group and 35% for the 300 mg group.

Regarding overall triazole use, an AUC_{24}/MIC of 20–25 is associated with satisfactory outcomes for both fluconazole-susceptible and -resistant strains.51,52,83,84 Similar to the other azoles, the best predictor of treatment efficacy with voriconazole in a murine model of candidiasis was AUC/MIC.85 In this study, the data relating AUC to MIC had the strongest relationship with an R^2 of 82%, while the relationship between peak/MIC and t > MIC (both related to efficacy) was not as strong (R^2 of 63% and 75%, respectively). As with other azoles, limited data in humans are available to establish relationships between voriconazole serum drug concentration and clinical outcome. According to the Food and Drug Administration (FDA)-approved product information for voriconazole, analysis of six
studies failed to demonstrate a correlation between serum concentration and efficacy. In contrast, a report examining treatment outcomes in 28 patients who had at least one voriconazole serum concentration determined while on therapy suggested such correlations may exist. In this report, all 10 patients with random voriconazole concentrations above 2.05 mg/L experienced a positive clinical outcome in contrast to documented disease progression and death occurring in 8 of 18 with concentrations <2.05 mg/L (P < 0.025). Eleven patients had their voriconazole dose increased due to a concentration <2 mg/L and eight of these patients survived. In a previous report of patients with aspergillosis treated with voriconazole, it was noted that three out of the five patients with serum voriconazole concentrations consistently <0.250 mg/L failed to respond to therapy, one deteriorated then subsequently improved with an increased dose and one had a stable response.

Associations between adverse events and voriconazole serum concentrations have also been examined. An analysis of 10 studies summarized in the voriconazole product information reported a positive correlation between elevations in serum concentration with liver function test abnormalities and visual disturbances. In the study of patients with aspergillosis treated with voriconazole, 6 of 22 patients with plasma concentrations >6 mg/L experienced liver failure or deterioration in liver function. Unfortunately, the timing of these serum concentrations in relation to dose administration is unclear. Also 15 of 137 patients developed abnormal vision shortly after dosing, which lasted for a few minutes. Although the abnormal vision was not directly attributed to elevated serum concentrations, the time frame of occurrence correlates with the time of the suspected peak concentration. The visual disturbances generally diminished with continued dosing and did not cause discontinuation of therapy in any of the patients. Increases in aspartate transaminase (r = 0.50; P = 0.0009) and alkaline phosphatase levels (r = 0.34; P = 0.03) were correlated with elevations of plasma voriconazole concentrations in adult allogeneic stem cell transplant recipients.

Serum concentrations in this analysis ranged from <1 to >6 mg/L. However, it was unclear whether the liver dysfunction was caused by elevated voriconazole concentrations or by other concomitant disease states or medications. Although accurate measurement of voriconazole concentrations is best completed with HPLC, bioassays have also been developed. Such assays, however, are not routinely available in most institutions. The available information suggests that, because of high inter-patient variability in voriconazole serum concentrations and potential relationships between such concentrations and both efficacy and safety, it may be clinically useful to monitor steady-state serum concentrations in select patients with serious IFIs. Guidelines for the treatment of histoplasmosis also suggest that serum concentration monitoring of voriconazole may be beneficial due to wide inter-patient variability and the potential for drug–drug interactions. Based on limited data available to date, a target level between 2 and 6 mg/L would be reasonable to ensure efficacy and limit toxicity, respectively. Although the timing of such concentrations is unclear, this range most likely represents trough and peak concentrations, respectively. Potential patient populations with indications for therapeutic drug monitoring include patients with progressive disease while on therapy, patients exhibiting signs or symptoms of significant toxicity (elevated hepatic enzymes or continued visual disturbances), patients on concomitant medications with significant drug interactions or patients in whom compliance with therapy is questioned.

**Posaconazole.** Posaconazole is the newest broad-spectrum triazole to gain approval by the FDA. Currently it is only available in an oral suspension and is approved for the prophylaxis of IFIs in high-risk patients and the treatment of oropharyngeal candidiasis. Without a parenteral formulation commercially available, posaconazole is dependent on oral absorption. Absorption is increased 2.6–4 times when the oral suspension is administered with a meal; with high-fat meals (~50 g of fat) enhancing absorption to the greatest extent.

Similar to many of the other azole antifungal agents, posaconazole is associated with significant inter-patient variability in pharmacokinetic parameters. In a study of 98 patients with persistent febrile neutropenia or refractory IFIs, exposure to posaconazole was 52% lower in allogeneic haematopoietic stem cell transplant recipients than non-bone marrow transplant patients. Owing to the many medications that bone marrow transplant patients receive, drug interactions could clearly be responsible for the lower drug exposure in this group. Mucositis could also be responsible for decreased drug exposure. However, due to concern regarding this potential effect, subjects were initially stratified to their respective treatment arm according to mucositis grade. Unfortunately, due to the low occurrence of grade 3 or 4 mucositis (n = 11), an adequate pharmacokinetic evaluation could not be completed. The mean steady-state peak concentrations were 0.851, 0.579 and 0.361 mg/L for the 400 mg twice daily, 600 mg twice daily and 800 mg daily treatment groups, respectively. However, for each group these mean values were shown to be highly variable, with reported coefficient of variations of 71% to 82%. In a study conducted in neutropenic stem cell transplant recipients, variability in the reported pharmacokinetic parameters ranged from 38% to 68% for all dosing groups. The 200 mg daily, 400 mg daily and 200 mg four times daily groups produced average steady-state peak serum concentrations (± SD) of 0.263 (± 0.202), 0.352 (± 0.166) and 0.479 (± 0.194) mg/L, respectively.

The pharmacodynamic effects of posaconazole have been studied in a neutropenic murine model of disseminated *C. albicans*. Similar to the other azole compounds, treatment efficacy was most related to the AUC/MIC ratio. Few human studies have been published which link posaconazole serum concentrations with clinical outcomes. An open-label multicentre study of the efficacy and safety of posaconazole for the treatment of invasive aspergillosis in patients who were refractory to or intolerant of other antifungal therapy reported that higher plasma concentrations were associated with improved response rates. During this study, posaconazole was dosed as 200 mg orally four times daily while in the hospital and 400 mg twice daily as an outpatient. When the mean maximum and average plasma concentrations were 0.142 and 0.134 mg/L, respectively, only 24% (4 of 17) of patients responded. Over 50% (18 of 34) of patients responded to therapy when the mean maximum and average plasma concentrations ranged from 0.467 to 0.852 mg/L and 0.411 to 0.719 mg/L, respectively. In contrast, when the mean maximum and average plasma concentrations rose to 1.48 and 1.25 mg/L, respectively, 75% (12 of 16) of the patients responded. This difference in apparent efficacy between those with the lowest plasma concentrations and those with the highest plasma concentrations may be explained in part by differences in the proportion of patients with a history of gastrointestinal dysfunction, total parenteral nutrition use or impaired dietary intake, or compliance with <90% of the scheduled doses.
Treatment-related adverse reactions included gastrointestinal effects, elevated liver function tests and rash and these were not correlated with elevated serum concentrations of posaconazole.94

The FDA-approved posaconazole product information includes a section on an exposure–response relationship. Although details are not provided, an association between average posaconazole concentrations and prophylactic efficacy is referenced.95 It is also reported that lower concentrations may be associated with an increased risk of treatment failure. For this reason, the prescribing information includes recommendations to enhance oral absorption and optimize plasma concentrations. These recommendations include administration of posaconazole with a full meal or nutritional supplement, avoidance of medications known to decrease posaconazole concentrations and enhanced monitoring for breakthrough infections in patients with the potential for decreased posaconazole concentrations (including those with severe nausea and vomiting).89 In the European Union prescribing information, a pharmacodynamic/pharmacokinetic association was described, which relates clinical outcome to total posaconazole exposure (AUC) divided by MIC.95 Specifically, a critical ratio of total drug AUC to MIC of ~200 was identified as being associated with a positive clinical outcome in patients treated with posaconazole for Aspergillus infections. Based on the available literature, it is difficult to define specific target peak and trough concentrations. However, it is clear from the prescribing information and clinical studies that a correlation between efficacy and enhanced drug exposure exists. Therefore, the European Union prescribing information also emphasizes the importance of ensuring adequate posaconazole absorption and plasma concentrations specifically when treating Aspergillus infections.

HPLC and bioassays have been developed to monitor posaconazole serum concentrations.96 No relevant biologically active metabolites have been detected and while there is currently no commercially available HPLC assay, HPLC will likely be the assay of choice when available.94,96,97 Treatment guidelines for histoplasmosis indicate that steady-state posaconazole serum concentrations may be beneficial due to wide inter-patient variability and potential drug–drug interactions.29 Based on the limited data available, reasonable target serum concentrations would be a maximum plasma concentration (Cmax) of >1.48 mg/L or an average serum concentration of >1.25 mg/L, after ~5–7 days of therapy. See Note added in proof. Potential patient populations with indications for therapeutic drug monitoring include patients with progressive disease while on therapy, patients on concomitant medications with significant drug interactions, patients with suspected poor oral absorption or patients in whom compliance with therapy is questioned. Additionally, prospective serum concentration monitoring may be considered for patients with severe IFIs or patients with questionable oral absorption.

Echinocandins

Echinocandins are the newest class of antifungal agents available and currently include caspofungin, micafungin and anidulafungin. These agents are only available intravenously. Compared with many other available antifungal medications, these agents are associated with few adverse events and are generally well tolerated by patients. While the FDA-approved indications for these three agents vary, they are generally utilized for the treatment of oesophageal candidiasis,98–100 candidaemia,101,102 invasive candidiasis103,104 and invasive aspergillosis in patients who are not responding or tolerating initial therapy103 and for the prophylaxis of fungal infections in immunocompromised patients.104,105

Although pharmacodynamic studies of the echinocandins in humans are limited, in vitro and animal studies have been completed. Early in vitro data suggest a concentration-dependent fungicidal or fungistatic relationship against several Candida species with caspofungin.106 A study of caspofungin in a murine model of invasive pulmonary aspergillosis demonstrated concentration-dependent activity that was measured by pulmonary fungal burden.107 However, a paradoxical effect on fungal burden was seen with caspofungin at the highest studied doses (4 mg/kg). The clinical significance of this finding, however, is not currently known. Early studies of echinocandin pharmacodynamics suggest that the AUC/MIC ratio108 or the Cmax/MIC ratio109 may be the best predictor of caspofungin efficacy.

To date, sufficient data are lacking in humans to indicate a relationship between toxicity or clinical efficacy of the echinocandins and serum concentration. Further studies are needed to explore the possible relationship between echinocandin concentration and clinical efficacy or associated toxicity. At this time, there is no defined role for therapeutic monitoring of the echinocandins.

Conclusions

Serum concentration monitoring of antifungals is gaining clinical importance and therefore recommendations for target serum concentrations and other monitoring guidelines have been summarized. Table 1 provides a review of these recommendations. Serum concentration monitoring may be completed for many different reasons. Generally, a correlation has been defined relating serum concentration to either efficacy or toxicity. Monitoring can also become important when a medication exhibits significant inter- or intra-patient variability in pharmacokinetic parameters, such as with itraconazole, voriconazole and posaconazole. Until recently, however, fluconazole and possibly itraconazole were the only antifungals that were routinely monitored by clinicians with serum concentrations. A role for the serum concentration monitoring of voriconazole and posaconazole is developing and is linked to a correlation between serum concentration and clinical efficacy. Currently there is no defined role for therapeutic monitoring of the echinocandins. However, this may develop with more research and increased clinical experience. Finally, as clinical efficacy has been related to dose with both fluconazole and amphotericin B, it is unlikely that therapeutic drug monitoring of these two medications will prove to be clinically useful. With the increasing incidence of IFIs and a growing number of antifungal agents, it is important for clinicians to have a good understanding of appropriate drug monitoring that may include selected serum concentrations.

Note added in proof

An analysis of data performed by the US FDA’s Center for Drug Evaluation and Research109 suggests a relationship exists between posaconazole exposure (as reflected by plasma
concentrations) and prophylactic efficacy. Proven or probable IFI were reported in two pivotal Phase 3 studies (Study C7198-316 and P01899) to be 6.52% and 3.87% (respectively) with mean concentrations ≤0.700 mg/L, and 1.88% and 0% (respectively) when concentrations exceeded 0.700 mg/L. The proposed target in this report was a posaconazole plasma concentration of >0.350 mg/L 3–5 h after dosing on day 2 of therapy with 200 mg given orally three times a day, in order to predict a target concentration of >0.700 mg/L 3–5 h after dosing on day 7. Such detailed information, however, does not appear in the product information currently approved.

Transparency declarations

M. L. G.; none to declare. R. H. D.; support from Merck (consultant), Schering-Plough (research, speaker’s bureau, consultant), Astellas (continuing medical education programme support), Ortho-McNeil (speaker’s bureau) and NeuTec (research support).

References


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