Terbinafine in combination for the treatment of resistant or refractory mycoses:
Investigating optimal dosing regimens using a physiologically-based pharmacokinetic model

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Abstract

Terbinafine is increasingly used in combination with other antifungal agents to treat resistant or refractory mycoses due to synergistic in vitro antifungal activity; high doses are commonly used but limited data are available on systemic exposure and no assessment of pharmacodynamic target attainment has been made. Using a physiologically-based pharmacokinetic (PBPK) model for terbinafine, this study aimed to predict total and unbound terbinafine concentrations in plasma with a range of high dose regimens, also calculating predicted pharmacodynamic parameters for terbinafine. Predicted terbinafine concentrations accumulated significantly during the first 28 days of treatment; AUC/MIC ratios and fAUC/MIC ratios increased by 54 – 62% on day 7 of treatment, and by 80 – 92% on day 28 compared to day 1, depending on dose regimen. Of the high dose regimens investigated, terbinafine 500 mg taken every twelve hours provided the highest systemic exposure; on day 7 of treatment predicted AUC, C_{max} and C_{min} were approximately 4-, 1.9- and 4.4-fold higher than with a standard dose regimen of 250 mg once daily. Close agreement was seen between PBPK model predicted and observed terbinafine concentrations, indicating good predictive performance. This study provides the first report of predicted terbinafine exposure in plasma with a range of high dose regimens.
The allylamine antifungal terbinafine is a well-established agent in the treatment of onychomycosis (1). Owing to its broad antifungal spectrum, interest in terbinafine has expanded to include a range of cutaneous and subcutaneous mycoses such as sporotrichosis, eumycetoma and chromoblastomycosis (2-4), as well as in combination with other antifungal agents to treat resistant or refractory invasive fungal infections (IFIs) as described in numerous case reports (1, 5). In support of the latter indication, synergistic in vitro antifungal activity has been demonstrated with terbinafine in combination with azole antifungals for many important fungal pathogens, including *Aspergillus* spp., *Zygomycetes*, *Fusarium* spp., *Paecilomyces* spp., *Candida albicans*, dematiaceous molds and the highly resistant *Scedosporium prolificans* (6-11).

High dose is a consistent feature of terbinafine use in these indications, with daily doses of up to 1000 mg daily (1), compared to the standard dosing regimen of 250 mg daily in onychomycosis, used to boost the plasma concentrations of terbinafine, which are known to be low following standard dosing due to extensive accumulation in skin and adipose tissue (12). However, no studies have assessed the systemic exposure of higher dose terbinafine treatment (>250 mg daily) or divided daily doses (q12h or q8h), factors that are likely to be crucial to the utility of terbinafine in effectively treating systemic mycoses in combination with other antifungals. This paucity of pharmacokinetic data is particularly important for terbinafine due to its very long terminal elimination half-life (2-3 weeks (13)) and substantial accumulation in plasma over time; trough terbinafine concentrations are known to accumulate >10-fold over 12-20 weeks following 250 mg once daily (14), with the majority occurring in the first 4 weeks of therapy (13).
In the absence of observed experimental concentration-time data at higher doses, physiologically-based pharmacokinetic (PBPK) models are a useful tool to accurately predict drug exposure (15). Using a PBPK model for terbinafine, this study aimed to predict terbinafine concentrations in plasma for a range of high dose regimens, also assessing the time above MIC achieved with each regimen to inform the optimal terbinafine dosing regimen in the treatment of refractory or resistant mycoses.

Materials and Methods

High dose terbinafine regimens investigated in this study (250 mg q12h, 250 mg q8h, 500 mg q24h and 500 mg q12h) were selected based on clinical use reported in clinical trials investigating the use of terbinafine for cutaneous and subcutaneous mycoses (2-4) and case reports of resistant or refractory mycoses (1, 5).

The dosing simulations in this study used a modified version of a previously reported PBPK model for terbinafine (12). Briefly, the model is comprised of several tissue compartments to reflect human physiology, with each compartment associated with a terbinafine-specific tissue-to-plasma partition coefficient and experimentally derived values for organ volume (L) and blood flow (L/h). The ability of this PBPK model to predict terbinafine pharmacokinetics in humans has been demonstrated (12).

In this study the oral absorption rate constant was set to 1 h⁻¹ for 250 mg doses and 0.7 h⁻¹ for 500 mg doses to reflect the less than proportional increase in peak terbinafine concentrations reported with single doses ≥ 500 mg (16). To accurately predict the prolonged accumulation of terbinafine, the previously low estimate of
volume of adipose tissue in the model (10 L) was increased (20 L (17, 18)). Dosing simulations using the human PBPK model considered five terbinafine dosing regimens, over three dosing durations (day 1, day 7 and day 28) with a focus on three key pharmacokinetic metrics, \( C_{\text{max}} \), \( C_{\text{min}} \) and AUC, for bound and unbound terbinafine concentration. Dosing simulations were performed with the Scientist software program (version 3.0; Micromath Scientific Software, Salt Lake City, Utah). Further analysis was performed in Microsoft Excel 2010.

Pharmacodynamic parameters that are predictive of drug efficacy including AUC/MIC, time above MIC and \( C_{\text{max}}/\text{MIC} \) have been established for most antifungal agents (19); to the authors’ knowledge no studies have investigated pharmacodynamic parameters for terbinafine. Due to this, AUC/MIC and \( C_{\text{max}}/\text{MIC} \) ratios, and time above MIC were investigated in this study, with each of these parameters assessed for both total terbinafine plasma concentration (bound to plasma proteins and unbound) and unbound terbinafine plasma concentration (free). Predicted pharmacodynamic parameters were calculated on day 1, day 7 and day 28 of treatment for each terbinafine dosing regimen to investigate the effect of drug accumulation. AUC/MIC and \( fAUC/\text{MIC} \) ratios were calculated using the linear trapezoidal rule for the AUC_{0-24h} corresponding to each day of treatment investigated. Plasma protein binding of 99% was assumed for the calculation of unbound terbinafine concentrations and predicted pharmacodynamic parameters (20).
Results

Predicted total terbinafine exposure in plasma following high dose terbinafine regimens compared to standard dose (terbinafine 250 mg q24h) are shown in Figure 1, with predicted AUC, $C_{\text{max}}$, and $C_{\text{min}}$ for total and unbound terbinafine shown in Table 1. By day 7 of treatment, total terbinafine trough concentrations following 250 mg once daily reach 0.14 mg/L; trough terbinafine concentrations were approximately 2-fold, 2.2-fold, 3.8-fold and 4.4-fold higher for the terbinafine 500 mg q24h, 250 mg q12h, 250 mg q8h and 500 mg q12h regimens, respectively. Both the terbinafine 250 mg q8h and 500 mg q12h regimen result in total trough concentrations above 0.5 mg/L at day 7 of treatment. The highest peak terbinafine concentrations occurred with the 500 mg q12h regimen, reaching 2.8 mg/L and 3 mg/L on day 7 and day 28 of treatment, respectively.

Predicted AUC/MIC and $f_{\text{AUC}}$/MIC ratios following standard and high dose terbinafine regimens are shown in Figure 2. AUC/MIC and $f_{\text{AUC}}$/MIC ratios increased by 54 – 62% on day 7 of treatment, and by 80 – 92% on day 28 compared to day 1, depending on dose regimen. On day 7 of therapy, predicted AUC/MIC and $f_{\text{AUC}}$/MIC ratios were approximately 2-fold higher for the 500 mg q24h and 250 mg q12h regimens, and 3-fold and 4-fold higher for the 250 mg q8h and 500 mg q12h regimens respectively, compared to standard terbinafine dosing.

Predicted $C_{\text{max}}$/MIC and $f_{C_{\text{max}}}$/MIC ratios are shown in Figure 3. $C_{\text{max}}$/MIC and $f_{C_{\text{max}}}$/MIC ratios increased by 10 – 29% on day 7 of treatment, and by 15 – 43% on day 28 compared to day 1, depending on dose regimen. On day 7 of therapy, predicted $C_{\text{max}}$/MIC and $f_{C_{\text{max}}}$/MIC ratios were approximately 11%, 24%, 69% and...
91% higher for the 250 mg q12h, 250 mg q8h, 500 mg q24h and 500 mg q12h regimens respectively, compared to standard terbinafine dosing. The predicted time above MIC on day 1, day 7 and day 28 of treatment for both total and free terbinafine are shown in Figure 4. On day 1, the terbinafine 250 mg q8h and 500 mg q12h regimens resulted in time above MIC of close to 100% for MIC values up to 0.125 mg/L for total terbinafine concentrations, with T>MIC values of approximately 60% for free terbinafine concentrations at an MIC of 0.004 mg/L. By day 7 these regimens achieved 100% time above MIC for MICs of up to 0.5 mg/L for total terbinafine concentrations, whereas standard dosing resulted in a time above MIC of 19% at this threshold. For unbound terbinafine concentrations at day 28, time above MIC was 100% for MIC values up to 0.008 mg/L and 44% at an MIC of 0.015 mg/L with the highest dose regimen (500 mg q12h); standard dosing resulted in time above MIC of 14% and 1% at these thresholds.

As observed pharmacokinetic data is available for terbinafine at standard doses (250 mg once daily), the model predicted concentrations following this dose were compared with observed data to assess the predictive performance of the model. There was close agreement between predicted and observed terbinafine concentrations in plasma (13, 14, 16, 21, 22) (Figure 5).

Discussion

Using a PBPK model, this study provides the first report of predicted terbinafine exposure in plasma with a range of high dose regimens. Trough terbinafine concentrations accumulate significantly by day 7 of treatment, with peak concentrations accumulating to a lesser extent (Figure 1 and Table 1) (14).
Pharmacokinetic studies suggest that higher terbinafine exposure would be expected in older patients and those with renal or hepatic impairment, with lower exposure in smokers (23, 24).

The ability to provide optimal dosing recommendations for high dose terbinafine from this work is limited by the absence of studies investigating pharmacodynamic parameters that predict its antifungal efficacy. For antifungals where this parameter is known, dosing regimens may be adapted to maximise antifungal activity (19). Despite this, it is clear that terbinafine is increasingly used at high dose (1), and thus a practical approach is warranted for the selection of high dose terbinafine regimens. Of the dosing regimens investigated in this study, terbinafine 500 mg q12h achieves the highest trough and peak concentrations and AUC values in plasma, suggesting this terbinafine regimen would achieve the highest antifungal activity irrespective of the pharmacodynamic target (AUC/MIC, time above MIC or $C_{\text{max}}$/MIC).

Terbinafine is known to have an unbound fraction of approximately 1% in serum due to non-saturable binding to albumin and lipoproteins (20, 25). While there have been conflicting reports on the applicability of the unbound drug hypothesis to some highly bound azole antifungals (26), a marked increase in terbinafine MICs in serum compared to protein free media has been reported (25), suggesting that this assumption is appropriate for terbinafine. Therefore, it is likely that pharmacodynamic measures based on unbound terbinafine concentrations, such as $fAUC$/MIC, will more closely correlate with antifungal efficacy than total drug concentrations.
Ryder and colleagues have reported MIC values for 5 isolates of *Aspergillus* spp. for terbinafine in combination with other antifungals, determining terbinafine MIC values between 0.004 – 0.016 mg/L in combination with itraconazole and 0.016 – 0.125 mg/L with voriconazole (27). At an MIC of 0.016 mg/L on day 7 of treatment, the predicted $f_{AUC}/MIC$ ratio for the highest dose regimen (terbinafine 500 mg q12h) is 20.55, compared to 5.19 with standard dose terbinafine. Further studies of terbinafine pharmacodynamics and the effect of protein binding on antifungal activity are needed to inform the clinical relevance of these findings.

While concentrations in important sites of infection such as brain remain undefined for terbinafine in humans, lung concentrations of terbinafine have been reported (28). In eleven patients who were administered terbinafine for 3 days prior to undergoing pulmonary lobectomy, concentrations in lung tissue were approximately 4-fold higher than those in plasma (28), indicating that therapeutic concentrations of terbinafine above pathogen MICs may be achievable in the lung. These findings suggest terbinafine may be a useful adjunct to azole antifungals in the treatment of refractory or resistant pulmonary mycoses (1).

The potent *in vitro* synergy observed between terbinafine and azole antifungals for a wide range of fungal pathogens enhances the potential role of terbinafine in the treatment of refractory IFIs (6-11). The complementary mechanisms of action of terbinafine and azoles, inhibiting squalene epoxidase and 14$\alpha$-lanosterol demethylase respectively, theoretically result in dual inhibition of fungal ergosterol production (29). These synergistic relationships are particularly important in the treatment of multi-resistant *Scedosporium prolificans*; several case reports have demonstrated *in vitro* synergy for terbinafine with other agents despite resistance to
all available antifungals, leading to successful combination therapy (30-33).

However, the choice of antifungal agents should be made cautiously as in vitro antagonistic interactions have been observed for both terbinafine and azoles when combined with amphotericin B for several isolates of *A. fumigatus* (6). An apparent limitation of the present study is the difficulty of linking PK/PD parameters to efficacy when synergism or antagonism is present in combination therapy; where synergistic relationships exist it is possible that low concentrations of terbinafine would be beneficial when combined with other agents.

An important concern with the use of high dose terbinafine is the relatively unknown safety profile. At regular doses (≤250 mg daily) terbinafine is generally well tolerated, although cases of hepatotoxicity have been reported (34). At higher terbinafine doses, a similar rate of adverse events has been reported in 401 patients receiving terbinafine 500 mg daily as those receiving 250 mg daily (5); more recently a trial in 63 patients of terbinafine 250 mg q12h versus 500 mg q12h in the treatment of sporotrichosis reported a slightly higher rate of adverse events in patients in the 500 mg q12h arm (2). Terbinafine is associated with fewer clinically significant drug interactions than azole antifungals, with the exception of medicines metabolised by CYP2D6 for which it is a known inhibitor (35).

The assessment of antifungal efficacy in animal models is particularly useful in the treatment of infection caused by relatively rare fungal pathogens, due to the poor feasibility of randomised controlled trials in humans (36). The combination of liposomal amphotericin B and terbinafine was recently found to prolong survival and reduce fungal burden in a murine model of disseminated *Fusarium verticillioides* infection (37). Further studies including terbinafine are needed in this area,
particularly in combination with first line azole antifungals such as voriconazole. Furthermore, future studies should address terbinafine pharmacodynamics, and the influence of the high protein binding observed with terbinafine on its antifungal efficacy. In light of the high mortality associated with resistant or refractory IFIs (38), synergistic interactions with other antifungals and case reports of clinical success, the use of high dose terbinafine in combination for the treatment of resistant or refractory IFIs appears promising and warrants further investigation.

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Conflicts of interest
MJD, VP, LP, AJM: None to declare.
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Table 1 Pharmacokinetic parameters for predicted total and unbound terbinafine plasma concentrations on Day 1, Day 7 and Day 28 for standard and high dose terbinafine regimens.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Terbinafine dose regimen</th>
<th>Day of therapy</th>
<th>Day 1</th>
<th>Day 7</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-24h&lt;/sub&gt;</td>
<td>[FAUC&lt;sub&gt;0-24h&lt;/sub&gt;] (mg.h/L)</td>
<td>Day 1</td>
<td>5.40 [0.0540]</td>
<td>8.30 [0.0830]</td>
<td>9.73 [0.0973]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 7</td>
<td>10.4 [0.104]</td>
<td>16.4 [0.164]</td>
<td>19.4 [0.194]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 28</td>
<td>10.8 [0.108]</td>
<td>16.6 [0.166]</td>
<td>19.5 [0.195]</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; &lt;br&gt; [FC&lt;sub&gt;max&lt;/sub&gt;] (mg/L)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Day 1</td>
<td>1.32 [0.0132]</td>
<td>1.46 [0.0146]</td>
<td>1.52 [0.0152]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 7</td>
<td>1.35 [0.0135]</td>
<td>1.61 [0.0161]</td>
<td>1.74 [0.0174]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 28</td>
<td>2.20 [0.0220]</td>
<td>2.46 [0.0246]</td>
<td>2.59 [0.0259]</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; &lt;br&gt; [FC&lt;sub&gt;min&lt;/sub&gt;] (mg/L)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Day 1</td>
<td>0.0332 [0.000332]</td>
<td>0.0659 [0.00659]</td>
<td>0.198 [0.00198]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 7</td>
<td>0.143 [0.00143]</td>
<td>0.308 [0.00308]</td>
<td>0.427 [0.00427]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 28</td>
<td>0.162 [0.00162]</td>
<td>0.288 [0.00288]</td>
<td>0.397 [0.00397]</td>
</tr>
</tbody>
</table>

For dose regimens where more than one dose is administered in a 24 hour period, C<sub>max</sub> and C<sub>min</sub> values for each day of therapy represent the average of C<sub>max</sub> and C<sub>min</sub> values for each dosing interval in the corresponding 24 hour period.

<sup>a</sup> For dose regimens where more than one dose is administered in a 24 hour period, C<sub>max</sub> and C<sub>min</sub> values for each day of therapy represent the average of C<sub>max</sub> and C<sub>min</sub> values for each dosing interval in the corresponding 24 hour period.
Figure 1 Predicted total terbinafine concentration-time profiles in plasma over the first 7 days of treatment using the PBPK model. The dashed line represents terbinafine dosed at 250 mg once daily (q24h) in each panel, with the solid line representing (1A) terbinafine 250 mg every 12 hours (q12h), (1B) terbinafine 250 mg every 8 hours (q8h), (1C) terbinafine 500 mg q24h and (1D) terbinafine 500 mg q12h.
Figure 2 Predicted AUC/MIC ratios for total and free terbinafine on day 1 (2A), day 7 (2B) and day 28 (2C) of treatment for standard and high dose terbinafine regimens.
Figure 3 Predicted $C_{\text{max}}$/MIC ratios for total and free terbinafine on day 1 (3A), day 7 (3B) and day 28 (3C) of treatment for standard and high dose terbinafine regimens.
Figure 4 Predicted percent time above MIC for total and free terbinafine concentrations on day 1 (4A), day 7 (4B) and day 28 (4C) of treatment for standard and high dose terbinafine regimens.
Figure 5 Predicted vs. observed terbinafine concentration-time profile following terbinafine 250 mg q24h for 28 days. The solid line represents the PBPK model predicted terbinafine concentration-time profile with closed symbols representing mean observed peak and trough terbinafine concentrations during the first 4 weeks of treatment reported in four pharmacokinetic studies. Observed data from (13) (closed triangles), (21) (closed diamonds), (16) (closed squares) and (22) (closed circles; reported in (14)). Symbol error bars represent the standard deviation of the observed concentrations; approximate SD calculated as range/4 for data from (21) as SD not reported.