Pharmacokinetic/pharmacodynamic analysis of voriconazole against Candida spp. and Aspergillus spp. in children, adolescents and adults by Monte Carlo simulation

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Abstract

The objective of this study was to investigate the cumulative fraction of response of various voriconazole dosing regimens against six Candida and six Aspergillus spp. in immunocompromised children, immunocompromised adolescents, and adults. Using pharmacokinetic parameters and pharmacodynamic data, 5000-subject Monte Carlo simulations (MCSs) were conducted to evaluate the ability of simulated dosing strategies in terms of AUC/MIC targets of voriconazole. According to the results of the MCSs, current voriconazole dosage regimens were all effective for children, adolescents and adults against Candida albicans, Candida parapsilosis and Candida orthopsilosis. For adults, dosing regimens of 4mg/kg intravenously every 12h (q12h) and 300mg orally q12h were sufficient to treat fungal infections by six Candida spp. (C. albicans, C. parapsilosis, Candida tropicalis, Candida glabrata, Candida krusei and C. orthopsilosis) and five Aspergillus spp. (Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus, Aspergillus niger and Aspergillus nidulans). However, high doses should be recommended for children and adolescents in order to achieve better clinical efficacy against A. fumigatus and A. nidulans. The current voriconazole dosage regimens were all ineffective against A. niger for children and adolescents. All voriconazole dosage regimens were not optimal against Aspergillus versicolor. This is the first study to evaluate clinical therapy of various voriconazole dosing regimens against Candida and Aspergillus spp. infections in children, adolescents and adults using MCS. The pharmacokinetic/pharmacodynamic-based dosing strategy provided a theoretical rationale for identifying optimal voriconazole dosage regimens in children, adolescents and adults in order to maximise clinical response and minimise the probability of exposure-related toxicity.

1. Introduction

The past two decades have witnessed a remarkable increase in the prevalence and severity of invasive fungal infections, which are associated with significant morbidity and mortality, mainly in immunocompromised and debilitated patients. Candida spp. and Aspergillus spp. are the major causes of invasive fungal infections [1]. The prevalence of invasive aspergillosis (IA) is increasing with the rise in the number of immunocompromised patients, including severely immunocompromised or critically ill children [2].

The second-generation antifungal triazole voriconazole was effective against a wide range of clinically significant fungal pathogens, including Aspergillus and Candida spp. [3]. Voriconazole was approved for use in the first-line setting for acute IA in 2002 owing to its favourable efficacy against Aspergillus spp. and few side effects [2]. Intravenous (i.v.) voriconazole and oral voriconazole are both recommended to treat patients with IA, candidaemia, disseminated infections caused by Candida spp., oesophageal candidiasis, etc. [4].

However, the pharmacokinetic behaviour of voriconazole is non-linear, and large interindividual and intra-individual variabilities have been observed in plasma concentrations. Small changes in dosage regimens may cause disproportionately large changes in the plasma concentrations of voriconazole [4,5]. Because of the complex pharmacokinetic behaviour of voriconazole and the narrow therapeutic window for the treatment of patients, it is necessary to assess various dosage regimens in order to maximise favourable clinical efficacy. Thus, a pharmacokinetic/pharmacodynamic (PK/PD) analysis should be used for evaluating, rationalising and optimising antifungal therapy. Monte Carlo simulation (MCS) is utilised as a valuable tool for determining dosage regimens and assisting in the selection for appropriate empirical antibiotic therapies. It is able to link pharmacodynamic data with the pharmacokinetic profile to predict the probability of a certain therapeutic outcome, thereby improving antimicrobial effectiveness and the quality of patient care [5].
Table 1
Summary of voriconazole pharmacokinetic parameters following voriconazole administration in children, adolescents and adults.

<table>
<thead>
<tr>
<th>Patient population</th>
<th>AUC0–24 (μg·h/mL)</th>
<th>AUC0–12 (μg·h/mL)</th>
<th>Cmax (μg/mL)</th>
<th>T1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childrena</td>
<td>4 mg/kg i.v. q12h</td>
<td>8 mg/kg i.v. q12h</td>
<td>9 mg/kg orally q12h (maximum of 350 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.92 (69)</td>
<td>29.2 (99)</td>
<td>15.7 (113)</td>
<td></td>
</tr>
<tr>
<td>Adolescentsb</td>
<td>4 mg/kg i.v. q12h</td>
<td>300 mg orally q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.4 (73)</td>
<td>16.7 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>4 mg/kg i.v. q12h</td>
<td>200 mg orally q12h</td>
<td>300 mg orally q12h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34.9 (53)</td>
<td>17.99 (53.7)</td>
<td>34.0 (53)</td>
<td></td>
</tr>
</tbody>
</table>

AUC0–12, area under the concentration–time curve from time zero to the end of 12-h dosing interval at steady-state; i.e., intravenous; q12h, every 12 h.

a Immunocompromised children (2 to 12 years old) and young adolescents (12–14 years old, weighing <50 kg).

b Immunocompromised adolescents aged 12 to <17 years.

c Value expressed as median ± standard deviation.

In this study, the probabilities of attaining optimal pharmacodynamic targets of various voriconazole dosage regimens against clinical isolates of Candida and Aspergillus spp. were calculated using an MCS technique in children, adolescents and adults.

2. Materials and methods

2.1. Pharmacokinetics

Data from three previously published studies on non-linear population pharmacokinetic (PPK) analysis of voriconazole conducted in children, adolescents and adults were applied [6–8]. In the study by Friberg et al., a PPK model was built by analysing the study design, study population and timing of plasma samples collected from five pharmacokinetic studies published previously, and exposure parameters of voriconazole in immunocompromised children (2 to <12 years old) and young adolescents (<12–14 years old, weighing <50 kg) were predicted [6]. In the study by Driscoll et al., an open-label, multiple-dose, multicentre study was conducted following i.v. voriconazole to oral switch regimens: 6 mg/kg i.v. every 12 h (q12h) on Day 1 followed by 4 mg/kg i.v. q12h, then switched to 300 mg orally q12h for immunocompromised adolescents (12 to <17 years old) [7]. The pharmacokinetic data of adults receiving a range of i.v. and oral voriconazole regimens were reported by Hope [8]. These three studies included the pharmacokinetic data of voriconazole in patients of different ages (2 to <12 years old, 12 to <17 years old and adults). The areas under the concentration–time curve at steady-state (AUCs) from the three studies, which were implied in the PK/PD model as voriconazole pharmacokinetic parameters, are summarised in Table 1.

2.2. Minimum inhibition concentration (MIC) distribution of Candida spp. and Aspergillus spp.

The MIC distribution data for Candida spp. were obtained from Cantón et al. [9]. In their study, six Candida spp. aggregated from 43 public tertiary-care hospital laboratories from January 2009 to February 2010 were tested by the Sensititre YeastOne method [9]. In another study reported by Espinel-Ingroff et al., discrete MIC distributions for six Aspergillus spp. from five independent laboratories in Europe and the USA were tested using the Clinical and Laboratory Standards Institute (CLSI) M38-A2 microdilution method [10]. The percentage MIC distributions of voriconazole for Candida spp. and Aspergillus spp. were calculated and were used for each simulation to calculate the cumulative fraction of response (CFR) (Table 2).

2.3. Monte Carlo simulation

MCS accounts for the variability in pharmacokinetic parameters as well as the MIC distribution in order to estimate the probability of achieving the pharmacodynamic target value of MICs/MIC (free-drug area under the concentration–time curve over 24 h/minimum inhibition concentration ratio) >25 in plasma [11]. In addition, other pharmacodynamic targets (1–50) were also evaluated for each simulation. To calculate free-drug concentrations of voriconazole, a value of 58% protein binding was used in all simulations [12].

Using pharmacokinetic parameters and pharmacodynamic data, MCSs were iterated from the 1st to the 500th subject using a commercially available risk analysis software (Crystal Ball® v.7.2.2; Decisioneering Inc.; http://www.crystalball.com) to estimate the probability of target attainment (PTA), defined as the percentage of subjects who achieved the requisite pharmacodynamic exposure (fAUC0–24/MIC) for each antibiotic dosage regimen/bacterial population combination. During simulations, pharmacokinetic parameters (AUCs) were assumed to follow a log-Gaussian distribution, and pharmacokinetic data (MICs) followed a discrete distribution. Protein binding of voriconazole was set as a constant value (58%). The CFR was calculated using weighted summation, with the following formula:

$$CFR = \sum PT(AMIC, pMIC)$$

The CFR at each MIC level was multiplied by the relative frequency of that MIC in the study population, p(MIC). A CFR...
expectation value of >90% was considered optimal for a dosage regimen against a population of organisms, as established previously by the OPTAMA programme [13].

3. Results

3.1. Probability of target attainment analysis

The probabilities of PK/PD target attainment by MIC for each voriconazole dosing regimen in children, adolescents and adults against six Candida spp. (from 1 to 50) were also simulated to calculate species-specific CFR expectation values. However, the simulated dosage regimens were ineffective against A. niger for immunocompromised children and adolescents. In addition, the simulated dosing regimens were not effective against Aspergillus versicolor, with CFR expectation values <90%.

Fig. 1. Probability of target attainment (PTA) of voriconazole against Candida spp. and Aspergillus spp. for each voriconazole dosing regimen in children, adolescents and adults. AUC/MIC, free-drug area under the concentration–time curve/minimum inhibition concentration ratio; i.v., intravenous; q12h, every 12 h; MIC, minimum inhibition concentration.

Overall, all of the simulated dosage regimens achieved CFR values of >90% in children, adolescents and adults against Candida albicans, Candida parapsilosis and Candida orthopsilosis. Immunocompromised children (2 to <12 years old) and young adolescents (12–14 years old, weighing <50 kg) had a voriconazole dosing regimen of 8 mg/kg i.v. q12h achieved high CFR values against Candida tropicalis, Aspergillus fumigatus and Aspergillus nidulans (91.84%, 90.48% and 90.01%, respectively). Immunocompromised adolescents (12 to <17 years old), both 4 mg/kg i.v. q12h and 300 mg orally q12h had an optimal likelihood of antifungal success against C. tropicalis, and 4 mg/kg i.v. q12h was sufficient for the patient against A. fumigatus. Moreover, 4 mg/kg i.v. q12h and 300 mg orally q12h in adults achieved ≥90% CFR against six Candida spp. (C. albicans, C. parapsilosis, C. tropicalis, Candida glabrata, Candida krusei and C. orthopsilosis) and five Aspergillus spp. (A. fumigatus, Aspergillus flavus, Aspergillus terreus, Aspergillus niger and A. nidulans). However, the simulated dosage regimens were ineffective against A. niger for immunocompromised children and adolescents. In addition, the simulated dosing regimens were not effective against Aspergillus versicolor, with CFR expectation values <90%.

Various PK/PD-related targets for Candida spp. and Aspergillus spp. (from 1 to 50) were also simulated to calculate species-specific CFR expectation values (Figs 2 and 3). The higher PK/PD targets represent the "worst-case" scenario, which may be important in some severe fungal infections where higher antimicrobial exposure may be required [14]. It is obvious that each CFR expectation value decreases with the increase in the PK/PD target.

Table 3 shows the assessment of CFR expectation values for various dosing regimens of voriconazole in children, adolescents and adults against six Candida spp. and six Aspergillus spp.

### Table 3
Cumulative fraction of response (CFR) expectation values (%) against six Candida spp. and six Aspergillus spp. for each voriconazole dosing regimen in children, adolescents and adults.

<table>
<thead>
<tr>
<th>Species</th>
<th>Children</th>
<th>Adolescents</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 mg/kg i.v. q12h</td>
<td>8 mg/kg i.v. q12h</td>
<td>4 mg/kg i.v. q12h</td>
</tr>
<tr>
<td></td>
<td>9 mg/kg orally q12h (maximum of 350 mg)</td>
<td>9 mg/kg orally q12h (maximum of 350 mg)</td>
<td>300 mg orally q12h</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>97.91</td>
<td>98.34</td>
<td>98.33</td>
</tr>
<tr>
<td></td>
<td>97.95</td>
<td>98.26</td>
<td>98.26</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>95.77</td>
<td>98.44</td>
<td>98.37</td>
</tr>
<tr>
<td></td>
<td>95.86</td>
<td>97.90</td>
<td>99.31</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>85.20</td>
<td>91.84</td>
<td>91.89</td>
</tr>
<tr>
<td></td>
<td>85.54</td>
<td>90.84</td>
<td>93.81</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>69.26</td>
<td>87.41</td>
<td>86.76</td>
</tr>
<tr>
<td></td>
<td>72.86</td>
<td>83.25</td>
<td>93.39</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>60.50</td>
<td>86.63</td>
<td>86.15</td>
</tr>
<tr>
<td></td>
<td>65.90</td>
<td>81.23</td>
<td>95.17</td>
</tr>
<tr>
<td>Candida orthopsilosis</td>
<td>96.22</td>
<td>99.06</td>
<td>99.09</td>
</tr>
<tr>
<td></td>
<td>96.36</td>
<td>96.65</td>
<td>96.70</td>
</tr>
</tbody>
</table>

A. fumigatus 67.05 90.48 71.18 90.54 86.52 97.73 73.97 97.65
A. flavus 52.34 85.10 60.50 84.43 77.34 97.24 64.18 97.14
A. terreus 54.97 85.38 62.27 84.80 78.39 96.41 65.71 96.31
A. niger 43.33 77.72 52.76 75.58 66.79 92.28 56.59 92.04
A. nidulans 77.31 90.01 79.20 89.05 86.05 95.17 80.76 95.03
A. versicolor 57.70 78.39 62.30 76.21 70.74 87.50 64.73 87.22

i.v., intravenous; q12h, every 12 h.
Fig. 2. Cumulative fraction of response (CFR) expectation values of various voriconazole dosage regimens at various fAUC/MIC (free-drug area under the plasma concentration–time curve over minimum inhibitory concentration ratio) targets against six Candida spp. (Candida albicans, Candida parapsilosis, Candida tropicalis, Candida glabrata, Candida krusei and Candida orthopsilosis) in children, adolescents and adults. i.v., intravenous; q12h, every 12 h.
Fig. 3. Cumulative fraction of response (CFR) expectation values of various voriconazole dosage regimens at various \( fAUC/MIC \) (free-drug area under the plasma concentration–time curve over minimum inhibitory concentration ratio) targets against six Aspergillus spp. (\( Aspergillus fumigatus \), \( Aspergillus flavus \), \( Aspergillus terreus \), \( Aspergillus niger \), \( Aspergillus versicolor \) and \( Aspergillus nidulans \)) in children, adolescents and adults. i.v., intravenous; q12h, every 12 h.
voriconazole dosage regimen of 4 mg/kg i.v. q12h against C. tropicalis achieved a CFR value of 90.3% at an AUC/MIC ≥15. When PK/PD target values of ≥25 and ≥35 were considered, the probability of achieving each value decreased to 85.36% and 80.22%, respectively (Fig. 2a). CFR expectation values at various PK/PD targets for each voriconazole dosage regimen in children, adolescents and adults against Candida and Aspergillus spp. are displayed in Figs 2 and 3.

4. Discussion

This is the first study evaluating the probability of voriconazole dosage regimens achieving their requisite PK/PD target by MCS using pharmacokinetic parameters and pharmacodynamic data against six Candida spp. and six Aspergillus spp. in children, adolescents and adults. The results of these simulations suggest that all of the dosage regimens simulated for children, adolescent and adults were effective against C. albicans, C. parapsilosis and C. orthopsilosis. Consistently, dosing regimens of 4 mg/kg i.v. q12h and 300 mg orally q12h were sufficient for adults to treat fungal infections by six Candida spp. (C. albicans, C. parapsilosis, C. tropicalis, C. glabrata, C. krusei and C. orthopsilosis) and five Aspergillus spp. (A. fumigatus, A. flavus, A. terreus, A. niger and A. nidulans). However, none of the simulated dosage regimens were effective against A. niger in immunocompromised children and adolescents. In addition, none of the voriconazole dosage regimens was effective against A. versicolor, with CFR expectation values of <90%.

The pharmacokinetic behaviour of voriconazole is complex and differs in children, adolescents and adults [15]. Voriconazole exhibits non-linear pharmacokinetics in adults owing to its capacity-limited elimination, and its pharmacokinetics are therefore dependent on the administered dose [3]. However, in contrast to observations in adults, the pharmacokinetic profile in children between 2 and 11 years of age appears to be linear following voriconazole doses of 3–4 mg/kg q12h [16]. In addition, paediatric patients have a much higher ability for elimination of the drug per kilogram of body weight than adults, resulting in a lower, potentially non-therapeutic exposure at similar dosages [16]. For this reason, relatively higher dosage regimens of voriconazole are required for paediatric patients than in adults to achieve similar plasma concentrations (the mean plasma AUC$_{0-12}$ for 8 mg/kg i.v. in children is approximately equivalent to 4 mg/kg i.v. in adults [17], and 4 mg/kg in children is approximately equivalent to adults administered a dosage of 3 mg/kg [16]).

In this study, the pharmacokinetic parameters of various voriconazole dosage regimens in children, adolescents and adults were obtained from three published studies [6–8]. These three studies included pharmacokinetic data of voriconazole in patients of different ages. PK/PK studies were conducted on pooled data from immunocompromised children, immunocompromised adolescents, or adults (including patients and healthy volunteers). It should be noted that young adolescents with a low body weight (<50 kg) during the transitioning period from childhood to adolescence (12–14 years old) should be dosed like children to achieve voriconazole exposures comparable with those of adults as described by Friberg et al and Driscoll et al [6,7].

Currently, the recommended voriconazole dosing regimen for children (2–11 years old) is 7 mg/kg i.v. twice daily (b.i.d.) and 200 mg b.i.d. for the oral suspension, without a loading dose [18]. For adolescents (>12 years old), the i.v. dosages are 6 mg/kg i.v. b.i.d. on Day 1 followed by 4 mg/kg i.v. b.i.d., and the oral dosages are 400 mg b.i.d. on Day 1 (200 mg b.i.d. for weight <40 kg) followed by 200 mg b.i.d. (100 mg b.i.d. for weight <40 kg) [16]. The recommended dosing regimen for adults is a standard loading dose of 6 mg/kg i.v. q12h on Day 1 followed by a maintenance dose of 4 mg/kg i.v. b.i.d. with the option to switch to an oral maintenance dose of 100 mg (<40 kg) or 200 mg (≥40 kg) b.i.d. For serious infections, the oral mainte-
nance dose may be increased from 200 mg to 300 mg (>40 kg) or from 100 mg to 150 mg q12h (<40 kg) [3]. In this PK/PD study, various maintenance dosage regimens (which are presented in Table 1) of voriconazole were evaluated to investigate whether they achieved effective treatment in children, adolescents and adults.

The PK/PD parameter for voriconazole has been characterised previously, demonstrating that the AUC$_{0-24}$/MIC ratio is the critical PK/PD parameter associated with treatment efficacy [11]. An in vivo study conducted with voriconazole in a murine candidiasis model showed that the voriconazole AUC$_{0-24}$/MIC ratios ranged from 11 to 58 (mean ± standard deviation, 24 ± 17; P = 0.45) [11]. However, many PK/PD-based simulations implied a value of AUC$_{0-24}$/MIC ≥25 as a predictor of voriconazole therapy [4,5,19]. Therefore, in this present study various PK/PD target values (1–50) were used to calculate CFRs of various voriconazole dosage regimens in children, adolescents and adults. The probability of treatment success can be obtained for any given target values from Figs 2 and 3.

Voriconazole has potent activity against a broad range of clinically significant fungal pathogens, such as Candida and Aspergillus spp., and is considered as the first-line therapy for treating IA [3,20]. Currently, voriconazole is also indicated for use in adolescents and adults for some invasive candidal infections, such as candidaemia in non-neutropenic patients [21]. However, the recommended oral dosage regimens of voriconazole monotherapy should not be administered empirically for treating Candida infections because of the azole cross-resistance among selected Candida [5,22].

There are two limitations to the present study. First, we did not consider other PK/PD surrogates such as trough serum concentration (C$_{min}$) >1 mg/L [23,24]. However, in the present study voriconazole dosage regimen in children, adolescents and adults. The probability of treatment success can be obtained for any given target values from Figs 2 and 3.

Voriconazole was evaluated using pharmacokinetic parameters and pharmacodynamic data by the MCS technique against Candida spp. and Aspergillus spp. in children, adolescents and adults. The results suggest that current simulated dosage regimens of voriconazole were all sufficient for children, adolescents and adults to treat fungal infections by C. albicans, C. parapsilosis and C. orthopsilosis. High doses should be recommended for children and adolescents to achieve better clinical efficacy against A. fumigatus and A. nidulans. However, none of the simulated voriconazole dosage regimens were effective against A. niger for children and adolescents. In addition, none of the current dosage regimens achieved optimal activity against A. versicolor. This PK/PD-based dosing strategy for Candida spp. and Aspergillus spp. infections provides a theoretical rationale for identifying optimal voriconazole dosage regimens in children, adolescents and adults. Further fungal infection studies and optimal dosage regimens of voriconazole should be designed for maximising clinical response and minimising the probability of exposure-related toxicity.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

References