Clinical pharmacology and therapeutic drug monitoring of voriconazole
Veringa, Anette

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Fungi are ubiquitous; there are about five million different species of fungi worldwide. Most of these fungi are innocuous for healthy individuals. However, some are opportunistic and can cause invasive infections especially in immunocompromised patients [1]. In comparison with bacterial infections, these fungal infections are generally underestimated. However, the number of immunocompromised patients is increasing, predominantly by advances in medical treatment and more aggressive chemotherapy. Therefore, fungal infections have become an increasing threat for these patients.
1.1 Invasive fungal infections
Both yeasts and filamentous moulds can cause invasive fungal infections. Among invasive fungal infections, invasive candidiasis (for yeasts) and invasive aspergillosis (for moulds) are most common [2]. Other less commonly isolated fungi include Cryptococcus, Fusarium, Scedosporium and Rhizopus species [3,4].

Candida species are part of the normal human microbiome, present on skin and mucosal surfaces. In immunocompromised patients, as well as in surgical patients, colonisation of Candida species can result in candidemia, the most common form of invasive candidiasis [5, 6]. Risk factors for invasive candidiasis include indwelling vascular catheters, recent surgery, and the treatment with broad-spectrum antibiotics. Furthermore, the incidence of invasive candidiasis is high in patients in intensive care units. Despite improvement of treatment in invasive candidiasis mortality remains high, up to 40-50% [6,7].

Aspergillus species are wide-spread and can be found throughout the entire environment. They easily spread by air via sporulation [8,9]. In healthy individuals, inhalation of these airborne conidia is harmless. However, in immunocompromised patients the conidia can germinate and hyphae can be formed, which results in invasive aspergillosis [10]. Especially patients with prolonged neutropenia, allogeneic stem cell recipients, or patients who received a solid organ transplantation and are treated with immunosuppressive drugs are at risk for invasive aspergillosis [11]. Although antifungal prophylaxis is used to prevent invasive aspergillosis and despite improved and less toxic treatment of invasive aspergil-losis with newer antifungal drugs, morbidity and mortality remains significant [12].

1.2 Treatment of invasive fungal infections
For the treatment of invasive fungal infections, currently three classes of antifungal agents are available, including polyenes, azoles, and echinocandines. For optimal antifungal treatment it is crucial to select the right antifungal agent, since the antifungal spectrum differs between antifungals [13-15]. In Table 1 the antifungal spectrum is shown for multiple antifungal agents against several invasive fungal pathogens that are commonly observed in clinical practice [13-15].

---

For **optimal antifungal treatment**, it is crucial to select the right antifungal agent.
Table 1. Antifungal spectrum of activity for several antifungal agents against commonly observed invasive fungal pathogens in clinical practice (data merged from: Andes, 2013 [13]; Nett, 2016 [14]; Carmona, 2017 [15]).

<table>
<thead>
<tr>
<th></th>
<th>Polyenes</th>
<th>Triazoles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Candida spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. albicans</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>C. krusei</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>C. guilliermondii</td>
<td>−</td>
<td>±</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Aspergillus spp.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. fumigatus</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>A. flavus</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>A. terreus</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>A. niger</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>A. nidulans</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fusarium spp.</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Scedosporium spp.</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Mucorales</td>
<td>±</td>
<td>−</td>
</tr>
<tr>
<td>Blastomyces spp.</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Histoplasma spp.</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Coccioides spp.</td>
<td>+</td>
<td>±</td>
</tr>
</tbody>
</table>

Plus sign (+): good activity against the specified organism; plus/minus sign (±): moderate activity against the specified organism (resistance noted); minus sign (−): little or no activity against the specified organism.

aIncludes amphotericin B deoxycholate and lipid amphotericin B formulations. bLimited clinical data.

1.3 Clinical pharmacology and therapeutic drug monitoring

Another important factor for treatment optimisation is understanding a drug’s pharmacokinetic and pharmacodynamic properties. In pharmacokinetics the absorption, distribution, metabolism and excretion of a drug is described. The area under the concentration-time curve (AUC) over 24 hours (AUC₀₋₂₄) is most often used to determine the exposure to a drug. Pharmacodynamics describes the pharmacological effect of the drug on the microorganism and in the human body, including both efficacy and toxicity. Here, the minimum inhibitory concentration (MIC) is used to describe the potency of an antifungal agent against a fungal isolate. By combining the pharmacokinetic and pharmacodynamic properties of a drug, the pharmacological profile for the drug is described [16, 17]. The pharmacokinetic/pharmacodynamic (PK/PD) indices that are commonly used to determine optimal antifungal treatment are the ratio of AUC to the MIC (AUC/MIC), the percentage of time that drug concentrations exceed the MIC (T>₉₉₉) and the ratio of peak serum concentrations to MIC (peak/MIC) [17].

For several antifungal agents the clinical effect and occurrence of adverse events is associated with its serum concentration [13,18]. However, the pharmacokinetics of some antifungals, for instance voriconazole, can be highly variable in patients [19]. For drugs with such variable pharmacokinetics,
serum concentrations can be measured for treatment optimisation, also known as therapeutic drug monitoring (TDM). In general, TDM should be considered for drugs with variable pharmacokinetics, provided that efficacy and/or safety are associated with serum concentrations, and the response to treatment cannot be measured in a faster or more direct way [16].

Drug resistance to antifungals is increasingly recognised as an emerging global problem [20]. For instance, resistance in A. fumigates isolates has already been detected in all continents of the world [21]. As a result the PK/PD target cannot be achieved. Here, higher drug exposure is necessary to increase the chance of treatment success, while the risk of toxicity is increased. Therefore, TDM should be considered whenever drug resistance might play a role.

1.4 Aim of this thesis
Better understanding of the pharmacokinetic and pharmacodynamic variability of voriconazole, will help to improve the treatment with this drug. The aim of this thesis is to gain insight in the pharmacokinetic variability of voriconazole and find out the optimum dosing approach for this drug. Furthermore, we address the potential additional value of performing TDM for voriconazole in clinical practice.

1.5 Outline of this thesis
In Chapter 2, a general overview will be given for monitoring of anti-infective drugs by using liquid chromatography-tandem mass spectrometry (LC-MS/MS). PK/PD relationships of anti-infective drugs will be discussed as well as the role of TDM for anti-infective drugs. Subsequently we will discuss the use of LC-MS/MS as a fast and accurate technique to help optimise treatment. Lastly, we explore alternative matrices, as well as the added value of a proficiency testing programme.

In this thesis we focus on voriconazole, a second-generation triazole with broad-spectrum antifungal activity. It is considered as first-line treatment of invasive aspergillosis in adults [11, 22]. The mechanism of action of this antifungal agent is based on inhibition of cytochrome P450-dependant 14α-lanosterol demethylation, which results in interruption of the ergosterol synthesis. Although voriconazole shows fungicidal activity against some filamentous fungi, it is fungistatic for yeasts [23].
Voriconazole is available in both oral and intravenous formulation. After oral administration it is rapidly absorbed and bioavailability seems high in healthy volunteers (> 90%) [24]. Several studies suggest that the bioavailability is significantly reduced in patients [25, 26]. However, other factors than bioavailability may have influenced the results of these studies. Therefore, in Chapter 4 we study the effect of switching the route of administration on voriconazole serum concentrations in hospitalised patients using retrospective data and strict inclusion criteria.

The main route of elimination for voriconazole is via the liver, less than 2% is excreted unchanged in urine. After hepatic metabolism by several cytochrome P450 iso-enzymes, including CYP2C19, CYP2C9 and CYP3A4, the main metabolite voriconazole-N-oxide is formed [24]. In chapter 3a we discuss the additional value of the measurement of voriconazole-N-oxide concentrations. In the second part of this chapter (3b) we describe a method to analyse voriconazole and voriconazole-N-oxide concentrations using LC-MS/MS.

Voriconazole shows non-linear pharmacokinetics, probably caused by saturation of its metabolism. As a result, an increase in the administered dose is not linearly related to an increase in drug exposure [24]. Several studies have shown that the efficacy and safety of voriconazole are associated with its serum concentration [27]. However, the serum concentration is highly variable in clinical practice. This variability is not only seen between patients, but also within patients over time [28, 29]. Several factors are known to influence voriconazole serum concentrations, including age, CYP2C19 genotype, concomitant use of CYP450 inhibitors or inducers, and liver function [24, 30-32]. We hypothesise that voriconazole serum concentrations can also be influenced by severe inflammation, since several drug-metabolising enzymes are down-regulated in the liver during inflammation [33]. In Chapter 5 we prospectively study the effect of inflammation on voriconazole metabolism by measuring consecutive voriconazole and voriconazole-N-oxide concentrations. We additionally examine the effect of voriconazole metabolism for several different cytochrome P450 2C19 genotypes.

Voriconazole is also recommended as treatment of invasive aspergillosis in pediatric patients [34]. However, the pharmacokinetics of voriconazole in children differs from adults. In children < 12 years of age, the pharmacokinetics of voriconazole appears to be near linear, while in children ≥ 12 years of age voriconazole pharmacokinetics seems non-linear. Though, with higher voriconazole doses, non-linear pharmacokinetics can also be observed in children < 12 years of age [35]. As in adults, the voriconazole concentration is also very variable in paediatric patients and it remains difficult to understand this high inter- and intra-individual variability and to optimise voriconazole treatment in these patients [36]. In Chapter 6a we present a study that investigates whether inflammation could contribute to the variable voriconazole concentrations observed in children. In the second part of this Chapter (6b) we present a linked PK/PD mathematical model for true individualised treatment with voriconazole in children.
Since voriconazole shows variable pharmacokinetics and the serum concentration is associated with efficacy and safety, TDM of voriconazole has been suggested to improve treatment outcome and to avoid toxicity. In a recent meta-analysis a therapeutic range between 1.0-6.0 mg/L was proposed \[37\]. However, it is currently uncertain whether personalised voriconazole treatment by using TDM for all adult patients receiving this drug is superior to the standard voriconazole dosing regimen. Furthermore, the evidence to support the benefit of TDM is limited to a few studies, most of them uncontrolled. Therefore, in Chapter 7a multicentre, prospective, cluster randomised crossover clinical trial is presented to test if individualised treatment of voriconazole by using TDM in adult patients is superior compared with patients who receive the standard voriconazole dose without performing TDM.

In Chapter 8 the outcomes of the research in this thesis will be discussed and future perspectives are provided.
References


