Pharmacokinetics of antifungal drugs in severely ill patients

van Wanrooy, Marjolijn Johanna Petronella

CHAPTER 1

Introduction

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Invasive fungal infections are infections of the blood or in other normally sterile sites, mainly caused by *Aspergillus* or *Candida* species (1). These infections occur in particular in immunocompromised patients such as neutropenic patients, hematopoietic stem cell or solid organ transplant recipients and critically ill patients.

Even with the introduction of new antifungal agents morbidity and mortality of invasive fungal infections have remained high (2, 3). The numbers of patients at risk for invasive fungal infections are increasing due to increasing survival rates of cancer and transplant patients and a broad clinical use of new immunosuppressive agents (3). Therefore continued efforts are required to improve the currently daunting perspective of patients with invasive fungal infections (2).

Besides the development of novel antifungal agents there are other priorities for future research to improve the outcome of invasive fungal infections (2). A considerable part of these priorities focus on an earlier start of an adequate treatment by improved diagnostic tests, direct detection of fungal species and antifungal resistance, better risk prediction models to target surveillance, prophylaxis and rapid diagnostics more appropriately and mechanisms to ensure the attainment of maximal antifungal effect as quickly as possible (2). Other approaches consist of novel immunomodulatory treatments to maximize antifungal effect and minimize immune-mediated damage and fibrosis; and finally to build collaborative national and international programs for antifungal resistance surveillance (2).

From a pharmacist's perspective, the most obvious focus for research in the field of antifungal treatment is to ensure the attainment of maximal antifungal effect as quickly as possible, especially focusing on pharmacokinetics and therapeutic drug monitoring. More insight in the pharmacokinetics of antifungal agents in specific patient populations is mandatory to be able to achieve sufficient concentrations or exposure as soon as possible. Therapeutic drug monitoring can be of assistance to maintain sufficient concentrations of antifungal agents.

OBJECTIVE

The objective of this thesis is to improve understanding of the pharmacokinetics of antifungal agents in severely ill patients and in the application of therapeutic drug

monitoring in order to eventually improve the outcomes of these patients receiving antifungal treatment.

OUTLINE OF THE THESIS

The research described in this thesis focuses on two antifungal agents, anidulafungin and voriconazole. For anidulafungin relatively little information on pharmacokinetics and therapeutic drug monitoring is available, whereas for voriconazole, therapeutic drug monitoring has gained a solid position in daily practice. The research performed therefore is more explorative for anidulafungin and more daily practice based for voriconazole.

ANIDULAFUNGIN

Anidulafungin is a semi-synthetic echinocandin, a lipopeptide synthesized from a fermentation product of *Aspergillus nidulans*. The enzyme 1,3-β-D glucan synthase is selectively inhibited by anidulafungin, resulting in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall. Anidulafungin has shown fungicidal activity against *Candida* species and activity against regions of active cell growth of the hyphae of *Aspergillus fumigatus*. Anidulafungin is registered for the treatment of invasive candidiasis in adult non-neutropenic patients.

Anidulafungin is rapidly distributed after intravenous infusion and is extensively (99%) bound to plasma proteins. Anidulafungin undergoes slow chemical degradation at physiologic temperature and pH to a ring-opened peptide that lacks antifungal activity. This ring-opened product is subsequently converted to peptidic degradants and eliminated mainly through biliary excretion. No dosing adjustments are required for patients with renal insufficiency or hepatic impairment.

Even though echinocandins are first-line treatment of invasive candidiasis in critically ill patients, limited data are available on the pharmacokinetics of anidulafungin in this patient population (4). Anidulafungin has predictable pharmacokinetics in healthy volunteers; exposure is dose-dependent and there is a low inter-individual variability (5). In patients with fungal disease, anidulafungin clearance appeared to be approximately 30% higher in patients with invasive candidiasis than in patients

with esophageal candidiasis. The patients with invasive candidiasis were more severely ill than the patients with esophageal candidiasis (6).

To investigate anidulafungin pharmacokinetics an accurate and simple liquid chromatography-tandem mass spectrometry method was developed for quantification of anidulafungin with straightforward sample preparation. *(Chapter 2)* Subsequently a prospective open-label study was performed to determine anidulafungin concentrations and exposure in critically ill patients and explore a possible correlation with disease severity and plasma protein concentrations. *(Chapter 3)* With the extensive data derived from this study, a model was developed to estimate the individual anidulafungin exposure in critically ill patients using limited-sampling strategies. *(Chapter 4)*

VORICONAZOLE

Voriconazole is a triazole antifungal agent. An essential step in fungal ergosterol biosynthesis is inhibited by voriconazole, by inhibiting the cytochrome P-450-mediated 14 alpha-lanosterol demethylation (7). This results in a loss of ergosterol in the fungal cell membrane. Voriconazole is the first line treatment for invasive aspergillosis (8). Besides, voriconazole is registered for the treatment of candidemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*) and treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

Voriconazole is available for both oral and intravenous administration. Absorption of voriconazole is rapid and almost complete (96%) following oral administration and is reduced when administered with high fat meals (9). Plasma protein binding is estimated to be 58 % (9). Voriconazole is metabolized by the hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4 (9). The major metabolite of voriconazole is the N-oxide, which has minimal antifungal activity and does not contribute to the overall efficacy of voriconazole (9). Less than 2 % of the voriconazole dose is excreted unchanged in the urine (9).

Measuring voriconazole concentrations, in conjunction with other measures of clinical assessment, is recommended in the Infectious Diseases Society of America

guidelines, to evaluate potential toxicity or to document adequate voriconazole exposure (8). This can be justified because of the large inter- and intra-individual variability in voriconazole concentrations (10, 11) and the relation between voriconazole trough concentrations and efficacy and safety. A recent randomized controlled trial in mainly hematology patients showed the benefits of routine therapeutic drug monitoring of voriconazole, reducing drug discontinuation due to adverse events and improving the treatment response in invasive fungal infections (12). However studies investigating voriconazole therapeutic drug monitoring included only patients with voriconazole concentrations measured (13-16). No data are available on when voriconazole therapeutic drug monitoring is applied and when not. The application of therapeutic drug monitoring in daily practice on the intensive care was investigated in a retrospective study. *(Chapter 5)*

In daily practice, a large variability in voriconazole concentrations is observed, not only between patients (10), but also within individual patients (11). Polymorphisms of cytochrome P450 isoenzymes (17), impaired liver function (18), and drug-drug interactions (19) are known to influence voriconazole pharmacokinetics, but do not explain the observed variability completely. Therefore other factors may contribute to the variability of voriconazole pharmacokinetics. Infections or inflammatory stimuli can cause changes in the activities and expression levels of various forms of cytochrome P450 isoenzymes (20). As voriconazole is extensively metabolized by cytochrome P450 isoenzymes, inflammation may also be a contributing factor to the variability of the pharmacokinetics of voriconazole. Whether inflammation, reflected by C reactive protein concentrations, influenced voriconazole trough concentrations was investigated in a retrospective study. *(Chapter 6)*

Finally, a general discussion and perspectives for future studies are described in *Chapter 7* and a summary of the obtained results is presented in *Chapter 8*.

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