Pharmacokinetics of antifungal drugs in severely ill patients

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CHAPTER 8

Summary

Continued efforts are required to improve the currently daunting perspective of patients with invasive fungal infections. Even with the introduction of new antifungal agents morbidity and mortality of invasive fungal infections have remained high. 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.

Pharmacists could contribute to the improvement of antifungal treatment by ensuring attainment of maximal antifungal effect as quickly as possible, by improving the understanding and expanding the knowledge of the pharmacokinetics of antifungal agents in specific patient populations and to provide reliable therapeutic drug monitoring services.

Therefore the main objective of this thesis was to improve understanding of the pharmacokinetics of antifungal agents in severely ill patients. In addition the application of therapeutic drug monitoring was evaluated in order to eventually improve the outcomes of antifungal treatment. The research described in this thesis focused on two antifungal agents; anidulafungin for the treatment of invasive candidiasis and voriconazole, the first line treatment of invasive aspergillosis.

ANIDULAFUNGIN

For pharmacokinetic studies it is essential to be able to measure concentrations of the drugs of interest. Since the previously described methods had several limitations, we started with developing a method to measure anidulafungin. The challenge was to develop a method suited to measure all three echinocandins in one run. It appeared feasible to include caspofungin, but unfortunately not micafungin. Our efforts resulted in an accurate and simple liquid chromatography-tandem mass spectrometry method with straightforward sample preparation for anidulafungin and caspofungin. *(Chapter 2)*

Since the anidulafungin clearance seems to be higher in more severely ill patients a prospective open-label study was performed to determine anidulafungin concentrations and exposure in 20 critically ill patients with invasive candidiasis and explore a possible correlation with disease severity and plasma protein

concentrations. *(Chapter 3)* Anidulafungin exposure was low in our critically ill patients. The multiple linear regression analysis provided a significant correlation between anidulafungin exposure and total body water and bilirubin concentrations. No significant correlations were observed between anidulafungin exposure and disease severity or plasma protein concentrations. Concerns about a low anidulafungin exposure seemed unnecessary since this was accompanied by low MICs of the isolated *Candida* strains that resulted in favorable AUC/MIC ratios, based on EUCAST data. However we recommend considering determining the anidulafungin exposure in patients with less susceptible *Candida albicans* or *glabrata* strains to ensure adequate exposure.

Since obtaining a full concentration-time curve to determine the exposure is not always feasible or appropriate, the extensive data derived from the previous study was used to develop strategies to estimate the individual anidulafungin exposure in critically ill patients using one or a few samples. *(Chapter 4)*

First, a two-compartment model was developed in MW\Pharm using an iterative 2-stage Bayesian procedure. Limited sampling strategies were investigated subsequently using two methods; a Bayesian analysis and a linear regression analysis. Anidulafungin exposure can be adequately estimated with the concentration from a single sample drawn 12 hours after the start of the infusion either by linear regression or using a population pharmacokinetic model, not only in critically ill patients but also in less severely ill patients as reflected by healthy volunteers. Besides that limited sampling can be advantageous for future studies evaluating the pharmacokinetics and pharmacodynamics of anidulafungin, this strategy can also be applied in anidulafungin therapeutic drug monitoring in selected patients as described above.

VORICONAZOLE

Although routine therapeutic drug monitoring of voriconazole appears to be beneficial no data are available on the implementation of voriconazole therapeutic drug monitoring in daily practice. Therefore this was investigated in a retrospective study in patients admitted on the intensive care. *(Chapter 5)*

A retrospective chart review was performed for patients that started treatment with voriconazole that lasted for at least three days while admitted to an intensive care unit. Voriconazole trough concentrations were measured in 64 of the 84 patients receiving voriconazole treatment. Patients with and without concentrations measured differed significantly with respect to the duration of voriconazole treatment and intensive care admission. Even though voriconazole concentrations were measured in most patients we concluded that the performance of voriconazole therapeutic drug monitoring can still be improved to overcome problems encountered like timing of sampling, incompleteness of data on clinical context and lack of implementation of recommendations.

Ideally we would be able to explain the observed variability in the daily practice of voriconazole therapeutic drug monitoring, but unfortunately this is not possible at this moment. We investigated whether inflammation, reflected by C reactive protein (CRP) concentrations, might influence voriconazole trough concentrations. *(Chapter 6)*

A retrospective chart review was performed for patients with at least one steady state voriconazole trough concentration and a CRP concentration measured on the same day.

One hundred and twenty-eight patients were included. Linear regression analyses both unadjusted and adjusted for covariates gender, age, dose, route of administration, liver enzymes and interacting co-medication, showed a significant association between voriconazole and CRP concentrations. For every 1 mg/L increase in CRP concentration, the voriconazole trough concentration increased by 0.015 mg/L. We therefore concluded that inflammation, reflected by C-reactive protein concentration, is associated with voriconazole trough concentrations. Further research is necessary to assess if taking the inflammatory status of a patient into account can be helpful in therapeutic drug monitoring of voriconazole to maintain concentrations in the therapeutic window, thereby possibly preventing suboptimal treatment or adverse events.

In conclusion, the research performed contributes to the knowledge about the pharmacokinetics of antifungal agents in severely ill patients, but continued efforts

are required for improvement as described in *Chapter 7* such as clinical validation of AUC/MIC ratios for anidulafungin and a dosing algorithm or pharmacokinetic model for voriconazole. We suggest a multidisciplinary approach to improve diagnosis and treatment of invasive fungal infections, in clinical practice as well as in research. Collaborative networks of institutions prepared to share data would potentially importantly improve the speed and power to further enhance our scientific knowledge to improve the treatment of these severely ill vulnerable patients.