Pharmacokinetics and optimal exposure of antifungal drugs in critically ill patients

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Summary

With the growing number of immunocompromised and critically ill patients, as the result of aggressive cancer treatment and immunosuppressive treatment after organ and stem cell transplantation, the incidence of invasive fungal disease (IFD) such as invasive candidiasis (IC) and invasive aspergillosis (IA) has increased in recent years. In IC and IA, the fungus has entered the bloodstream and has spread throughout the whole body. These IFD are important causes of morbidity and mortality and are associated with a prolonged hospital stay and increased costs. Prompt initiation of antifungal therapy in the appropriate dose is required to improve outcome in patients with IFD. However, when drugs are registered, severely ill patients are usually not included in registration studies by the manufacturer of the drug. Hence it is often unknown if the recommended dose is also suitable for this patient group, since the behavior of the drug in the body (pharmacokinetics) and the blood concentration can be altered due to changes in absorption, distribution, metabolism, and clearance of the drug. The altered pharmacokinetics of drugs also applies to critically ill children and infants. Moreover, developmental changes in renal and hepatic function, the gastrointestinal tract, and body composition can contribute to a varying drug concentration with age. Children are typically not included in registration studies, due to ethical issues and technical challenges, and the recommended childrens dose is therefore extrapolated from the adult dose, which may result in decreased efficacy or toxic effects. In this thesis we have evaluated the pharmacokinetic parameters and the exposure of antifungal drugs and established the relation with the treatment outcome in critically ill adults and children. Furthermore, we have developed noninvasive sampling methods to facilitate therapeutic drug monitoring (monitoring of drug concentrations in blood/body fluids and subsequent dose adjustments, TDM).

In Chapter 2, in a retrospective study we have evaluated the exposure of the

antifungal drug fluconazole in 99 critically ill children. Besides, we have assessed the relation between the fluconazole blood concentration and the time to attain a negative culture (culture conversion). The study showed that the fluconazole concentration was considered subtherapeutic in 40% of the patients. The fluconazole exposure was significantly lower in pediatric cancer patients, with the currently recommended dosing regimen, compared to children with a different underlying condition (P = 0.003). Furthermore, a higher fluconazole concentration was significantly associated with a shorter time to culture conversion in these critically ill children. Hence, pediatric cancer patients do not achieve an adequate fluconazole exposure with the currently recommended dosing regimen and a higher fluconazole dose is required. We recommend the development of a new dosing strategy to achieve adequate fluconazole exposure in pediatric cancer patients. In addition, TDM of fluconazole can be a valuable tool to detect possible under-exposure in critically ill children. Children do often fear needles and can have difficult vascular access. In Chapter 3 we have developed and clinically validated a method of analysis to determine fluconazole in 21 oral fluid samples from pediatric patients. The fluconazole concentration in oral fluid was in good agreement with the blood concentration of fluconazole and samples were stable at room temperature for at least 17 days. Oral fluid sampling can be a noninvasive, painless alternative to perform TDM of fluconazole in children when blood sampling is not possible or desirable. When patients receive prolonged courses of antifungal treatment and use fluconazole at home, this method of analysis can extend the possibilities of TDM for patients at home.

In Chapter 4, we have evaluated the posaconazole exposure in 70 adult cancer patients and organ transplant recipients. We have detected risk factors for underexposure of posaconazole and assessed the relation between the posaconazole exposure and the treatment outcome. The posaconazole exposure was not sufficient in over 40% of patients with IFD, and those at risk for IFD, after administration of the posaconazole oral suspension. Risk factors for underexposure were a lack of enteral nutrition (patients who were not able to eat), a liquid diet, vomiting, use of medication that affects the pH of the stomach (such as a proton pump inhibitor (PPI) or H_2-receptor antagonist), and concomitant chemotherapy. Furthermore, a higher posaconazole concentration was significantly associated with a better treatment outcome. Based on the results of our study and other recent findings, we recommend that the posaconazole oral suspension is not prescribed to patients who are unable to eat or use a PPI/H_2-antagonist. With the new tablet and intravenous formulation, posaconazole is also suitable for patients with no food intake, absorption problems, and the use of concomitant medication that affects gastric pH. The different posaconazole formulations, in combination with TDM in case of the oral suspension, can

help to ensure sufficient posaconazole exposure and make posaconazole a valuable addition to the antifungal prophylaxis and treatment arsenal. To facilitate TDM of posaconazole and the other triazoles, we have developed and clinically validated a dried blood spot (DBS) analysis, using a finger prick instead of a venous blood sample in 28 patients (Chapter 5). DBS concentrations of posaconazole, fluconazole, and voriconazole were in good agreement with plasma concentrations and samples were stable at room temperature for at least 12 days. The majority of the patients preferred DBS sampling over venous blood sampling. Major advantages of DBS sampling were significantly less pain and not traveling to the hospital for blood sampling. With this DBS analysis, the possibilities of TDM of the triazoles can be extended to patients at home and to hospitals without an advanced bio-analytical infrastructure.

For the determination of caspofungin concentrations, we developed a method of analysis to measure caspofungin concentrations in blood in Chapter 6. Subsequently in Chapter 8, we have evaluated the pharmacokinetics and exposure of caspofungin in patients with (suspected) IC on the Intensive Care Unit (ICU) in a multicenter prospective intervention study. The interim analysis of this study showed that the caspofungin exposure in 10 ICU patients was low compared with the exposure in healthy volunteers and other (non-) critically ill patients, most likely as a result of a larger volume of distribution. Furthermore, the exposure was low in patients of 75 to 80 kg who received the standard dose of 50 mg (patients $>$ 80 kg receive a standard dose of 70 mg) and in patients suffering from severe liver damage who received a reduced caspofungin dose of 35 mg, which we previously also demonstrated in a case report (Chapter 7). Our findings suggest that these patients should perhaps initially receive a higher empiric maintenance dose. However, further research is needed to provide evidence for the development of new dosing recommendations for this patient group. With these dosing recommendations, and subsequent TDM in certain cases, an adequate caspofungin exposure can be achieved shortly after the start of the treatment with caspofungin in ICU patients.

In this thesis, we have shown that the antifungal drug exposure in critically ill adults and children is often inadequate with the standard dose. Adequate exposure is essential for efficacy, and ultimately, for improved outcome. Our findings call for the development of a more personalized therapy for patients with IFD (chapter 9). This treatment should be based on the characteristics of the fungus (type of fungus, minimum concentration that inhibits the growth of the fungus, and location of the infection) and on the characteristics of the patient (underlying disease and treatment of the disease, leading to altered absorption, distribution, metabolism, or clearance of the drug). Together these characteristics provide information on the appropriate antifungal treatment for the individual patient, leading to an optimal drug exposure

and avoiding unnecessary, ineffective, or toxic therapy. With this strategy, adequate antifungal treatment can be achieved with the current arsenal of antifungal drugs.