Clinical pharmacology and therapeutic drug monitoring of voriconazole
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Summary
The number of patients at risk for invasive fungal infections is increasing, because of an increasing number of immunocompromised patients. One of the most common mould infections is invasive aspergillosis, for which voriconazole is recommended as first line treatment. The pharmacokinetics of voriconazole is highly variable. Several factors are known to influence the pharmacokinetics of voriconazole, including age, CYP2C19 genotype, concomitant use of CYP450 inhibitors or inducers, and liver function. However, these factors do not fully explain the observed pharmacokinetic variability of voriconazole. Furthermore, voriconazole has a narrow therapeutic range. It is suggested to maintain the voriconazole trough concentration between 1 – 6 mg/L to improve treatment outcome and to avoid toxicity. Since the voriconazole trough concentrations is associated with efficacy and safety, therapeutic drug monitoring (TDM) of voriconazole has been suggested, although the evidence to support the benefit of TDM is limited to a few studies.

In this thesis, we investigated other factors, including inflammation and bioavailability, that could influence the pharmacokinetics of voriconazole besides the factors mentioned above. In addition, we explored how using pharmacodynamic parameters such as the galactomannan index could optimise treatment with voriconazole. Furthermore, we looked at the utility of TDM for voriconazole.

In Chapter 2, a review is presented for monitoring of anti-infective drugs by using liquid chromatography-tandem mass spectrometry (LC-MS/MS). In this Chapter pharmacokinetic and pharmacodynamic relationships of anti-infective drugs are discussed, along with the role of TDM for anti-infective drugs. Subsequently, we discussed the additional value of the LC-MS/MS for TDM of anti-infective drugs to optimise treatment, including the high sensitivity and selectivity of this analytical technique. Furthermore, we explored the use of other matrices than blood for TDM and alternative sampling strategies, including dried blood spot sampling.

To gain more insight in the pharmacokinetics of voriconazole we described in Chapter 3a the additional value of measuring the main metabolite of voriconazole, voriconazole-N-oxide. By measuring both voriconazole and voriconazole-N-oxide, more information can be obtained on the metabolic capacity of the liver for an individual patient. In addition, a distinction can be made between for instance an ultra-rapid metaboliser of voriconazole or non-compliance. Therefore, measuring both voriconazole and its metabolite may help TDM guided dosing to optimise voriconazole treatment in clinical practice.

In Chapter 3b an analytical method is described for therapeutic drug monitoring of voriconazole and its primary metabolite, voriconazole-N-oxide. By including both voriconazole and voriconazole-N-oxide, this analytical method is more informative for
switching the route of administration on voriconazole trough concentration. Thirteen patients were included in this retrospective cross-over analysis. For intravenous administration of voriconazole a mean trough concentration of 2.28 mg/L was found and for oral administration a mean of 2.04 mg/L ($P = 0.390$). The mean bioavailability of voriconazole was 83.0%, which is substantially higher compared with earlier studies. The results of our study therefore suggested that other factors apart from bioavailability may cause the observed difference in voriconazole trough concentrations between oral and intravenous administration.

During an infection or inflammation, several drug-metabolising enzymes in the liver are down-regulated, including cytochrome P450 iso-enzymes. Voriconazole is extensively metabolised by cytochrome P450 iso-enzymes. In Chapter 5 we describe a prospective observational study to determine the effect of inflammation on voriconazole trough concentration and metabolism in adult patients. To determine the degree of inflammation, C-reactive protein (CRP) concentrations were used. In this study thirty-four patients were included. A longitudinal data analysis was performed to assess the effect of inflammation on the metabolic ratio of voriconazole-N-oxide/voriconazole and on voriconazole trough concentration. We included 489 voriconazole trough concentrations in this analysis. The results of this study showed that inflammation significantly influenced the voriconazole trough concentration and the metabolic ratio, after correction of other factors that could influence voriconazole metabolism. The metabolic ratio was decreased by 0.99229, while the voriconazole trough concentration was increased by 1.005321, where $N$ is
the difference in CRP units (in mg/L). Therefore, frequent monitoring of voriconazole trough concentrations and CRP concentrations is recommended during and following severe inflammation.

In Chapter 6a we performed a retrospective chart review to determine the effect of inflammation on voriconazole trough concentration in children. Paediatric patients were divided into two groups based on their age: group 1 (< 12 years) and group 2 (≥ 12 to 18 years). CRP concentrations were used to determine the degree of inflammation and categorised in a low to moderately high (0–150 mg/L) and a high (> 150 mg/L) degree of inflammation. Eleven patients were included in group 1 and sixteen patients in group 2. For patients aged < 12 years, no significant difference was found between a low to moderately high and a high degree of inflammation (P = 0.682). However, in patients aged 12 – 18 years, a significantly higher voriconazole trough concentration was observed with CRP values > 150 mg/L compared to patients with CRP values of 0 – 150 mg/L (P = 0.027).

In conclusion, inflammation as reflected by CRP values, is associated with higher voriconazole trough concentrations in patients aged ≥ 12 – 18 years but not in patients aged < 12 years. The CRP value may therefore be helpful in TDM of voriconazole during severe infection for patients aged ≥ 12 – 18 years.

The galactomannan index is a routinely used diagnostic marker for invasive aspergillosis and is occasionally used for monitoring the clinical response to antifungal treatment. In Chapter 6b we developed a pharmacokinetic-pharmacodynamic (PK-PD) mathematical model in children that links the serum pharmacokinetics of voriconazole and the pharmacodynamics, quantified by using the circulating galactomannan concentrations. The pharmacokinetic and pharmacodynamic data from twelve children were studied, collected as part of routine clinical care. Since the data were necessarily sparse a previously described PK model was used as the Bayesian prior. Subsequently the PK-PD model was used to estimate the average area under the concentration time curve (AUC) in each patient and the time course of galactomannan concentrations. Additionally, the relationship between the ratio of the AUC to the concentration of voriconazole that induced half maximal killing (AUC/EC₅₀) and the terminal galactomannan concentration was determined. The terminal galactomannan concentration was strongly predicted by the (AUC/EC₅₀)/15.4 (P = 0.003), and patients with an AUC/EC₅₀ ratio of >6 showed a trend for a consistently lower terminal galactomannan concentration (P = 0.07). The construction of a linked PK-PD model is the first step in developing control software to enable true individualised treatment and to determine individualised concentration targets. By following galactomannan concentrations over time, a first critical step was made to maximise clinical response.

TDM of voriconazole is recommended based on retrospective data and limited prospective data. In Chapter 7 a multicenter (n = 10), prospective, cluster randomised, cross-over clinical trial in haematological patients ≥ 18 years, treated with voriconazole was performed to investigate if TDM guided treatment of voriconazole is superior to standard treatment. All patients received the standard voriconazole dose at start of the treatment and voriconazole trough concentrations were taken immediately after treatment initiation and were repeated over time.
In the TDM group the dose was adjusted as appropriate. In total 189 patients were enrolled. For the primary composite end-point, including response to treatment, and patients for whom voriconazole treatment was discontinued due to an adverse event related to voriconazole 28 days after treatment initiation, no significant difference was observed between both groups ($P = 0.681$). For this analysis 74 patients were included in the non-TDM group and 68 patients in the TDM group. In the TDM group however, significantly more voriconazole trough concentrations were found within the therapeutic range. Therefore, the results of this study suggest a more selective approach for TDM of voriconazole, rather than TDM for all patients treated with voriconazole. Here, severity of the fungal disease, drug susceptibility, the clinical condition of the patient and prior treatment with other antifungal agents should be taken into account.

The results of the research performed in this thesis are discussed in **Chapter 8** and future perspectives are presented. In conclusion, our findings provide more insight into the variable pharmacokinetics of voriconazole and give practical tools to improve voriconazole treatment in clinical practice. In addition, for true individualised and optimal treatment of voriconazole not solely the pharmacokinetics of voriconazole should be taken into account by performing TDM, but also a pharmacodynamic parameter to determine response to treatment. With this strategy, the treatment of voriconazole could be further improved.