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## Clinical pharmacology and therapeutic drug monitoring of voriconazole

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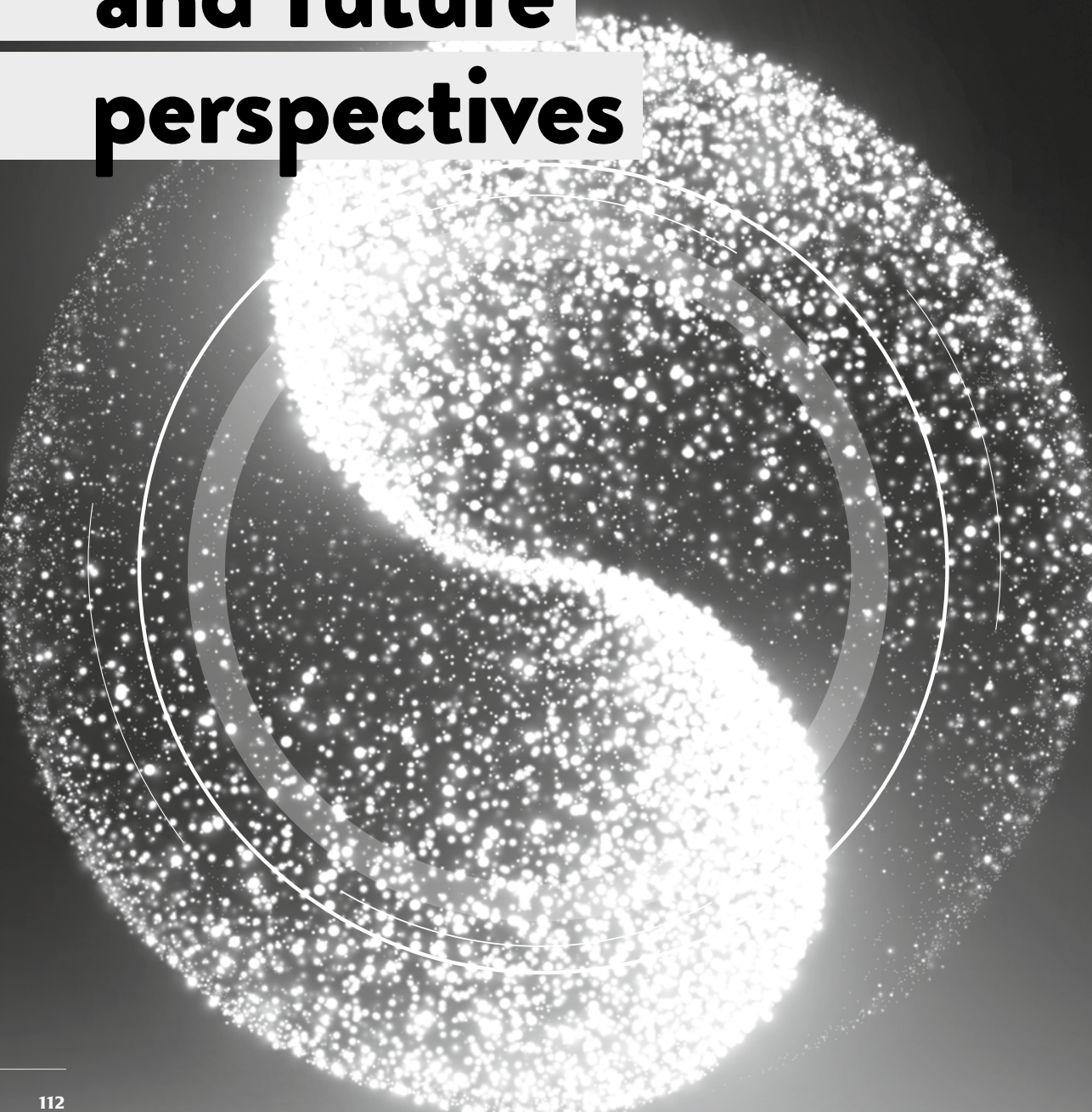
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**08**

**General discussion  
and future  
perspectives**



**Invasive aspergillosis is one of the most common mould infections. This is a life-threatening complication, which is frequently seen in immunocompromised patients [1,2]. Voriconazole, a broad-spectrum antifungal agent, is recommended as primary treatment in most patients with invasive aspergillosis [3]. The pharmacokinetics of voriconazole are highly variable, which complicates adequate treatment with this drug. Although a therapeutic range has been defined for voriconazole (1 – 6 mg/L) to optimise response to treatment and to avoid toxicity [3] it remains difficult to give a proper dosing advice, for instance because of the non-linear pharmacokinetics of voriconazole and a poor correlation between the voriconazole dose and the measured concentration [4,5].**

**Several factors have been described to influence the pharmacokinetics of voriconazole, including age, CYP2C19 genotype, concomitant use of CYP450 inhibitors or inducers, and liver function [6-9]. However, all these factors still do not fully explain the observed pharmacokinetic variability. In this thesis we have investigated which other factors could influence the pharmacokinetics of voriconazole. Furthermore, we have explored the additional value of performing therapeutic drug monitoring (TDM) for voriconazole in clinical practice. Additionally, we have explored how voriconazole treatment could be optimised, by determining which factors influence the pharmacokinetics of voriconazole.**

### **8.1 Pharmacokinetics of voriconazole**

First of all, to gain more insight in the pharmacokinetics of voriconazole, voriconazole-N-oxide concentrations can be measured besides voriconazole concentrations. Although voriconazole-N-oxide shows no antifungal activity [6], it gives more information on voriconazole metabolism. The additional value of measuring voriconazole-N-oxide concentrations is described in Chapter 3a. By measuring both voriconazole and voriconazole-N-oxide concentrations more information can be obtained on the metabolic capacity of the liver and is therefore helpful to interpret voriconazole levels and to optimise voriconazole treatment (see table 1). In Chapter 3b a fast liquid chromatography-tandem mass spectrometry (LC-MS/MS) method is described to deter-

mine the voriconazole-N-oxide concentration.

To determine whether voriconazole treatment is optimised by measurement of both voriconazole and voriconazole-N-oxide concentrations, this should be implemented in clinical practice. Subsequently, it should be examined whether measurements of both voriconazole and voriconazole-N-oxide results in better treatment guidance of voriconazole compared with measurement of solely voriconazole concentrations. In addition, with successive low voriconazole concentrations and high corresponding voriconazole-N-oxide concentrations, a switch to another second-line antifungal agent, such as posaconazole could be considered, especially in the initial and most critical phase of

of antifungal treatment. Next, it should be investigated if this strategy results in improved treatment outcome with acceptable costs.

Besides N-oxidation another major metabolic pathway in humans is the hydroxylation of voriconazole, where hydroxyvoriconazole and dihydroxyvoriconazole are formed [11]. Although serum concentrations of hydroxy-voriconazole and dihydroxyvoriconazole are low compared with voriconazole-N-oxide concentrations, the hydroxylation pathway seems to be more important than the N-oxidation pathway. The partial metabolic clearance via hydroxylation seems to exceed N-oxidation considerably [12,13]. Therefore, it should be further examined to what extent the conversion from voriconazole to voriconazole-N-oxide is sufficiently representative for the total metabolism of voriconazole in clinical practice. Additionally, with the currently available analysis techniques it remains challenging to accurately measure subtle changes for the observed low concentrations of hydroxy-voriconazole and dihydroxyvoriconazole. If an accurate method is available, more information could be obtained for the hydroxylation pathway, and the role of this pathway and the N-oxidation pathway in for instance drug interactions and other factors influencing the metabolic capacity of the liver.

A reduced bioavailability of voriconazole is suggested as a factor that contributes to variable voriconazole concentrations [14,15]. In adult patients the bioavailability of voriconazole is high, over 90% [6]. In Chapter 4, we showed that the bioavailability of voriconazole in hospitalised patients is slightly reduced (83%) compared with the reported bioavailability of > 90%, mostly studied in healthy volunteers [6]. However, the observed bioavailability in our study is considerably higher compared to other studies [14,15]. In contrast to these studies, we used strict inclusion criteria. For instance, each patient served as his/her own control and other clinical parameters potentially influencing voriconazole concentrations had to be comparable. These strict inclusion criteria were used to minimise confounding. Therefore, it seems that other factors apart from bioavailability contribute to the variable voriconazole concentrations. For instance, poor metabolisers of CYP2C19 could have higher bioavailability compared with extensive metabolisers. This is probably due to a reduced first-pass metabolism caused by a decreased CYP2C19 activity in the gut wall. In addition, for ultra-rapid metabolisers bioavailability could be reduced based on higher CYP2C19 activity in these patients [12,16]. This hypothesis should be prospectively confirmed in a larger patient population. The results of our study however emphasise the

**Table 1.** Voriconazole/voriconazole-N-oxide concentrations in relation to typical clinical situations [10].

	Low voriconazole	High voriconazole
Low voriconazole-N-oxide	Non-compliance Malabsorption	Poor metaboliser/intermediate metaboliser Hepatic impairment DDI: CYP450 inhibitor Inflammation
High voriconazole-N-oxide	DDI: CYP450 inducer Ultra-rapid metaboliser	Overdose

need for the input of an expert with knowledge of factors influencing the pharmacokinetics of voriconazole if a patient is treated with this drug. Although the switch from intravenous to oral antifungal treatment is encouraged in antimicrobial stewardship programmes (ASPs) to reduce costs [17], the condition of the patient remains an important factor whether this switch is clinically appropriate. For instance, in hematologic patients gastro-intestinal complications are commonly observed. Therefore in ASPs, guidelines should be included for specific patient populations. In this guideline patient characteristics of this population should be highlighted and taken into account to optimise treatment. Furthermore, ASPs mainly focussing on antifungal agents are limited. In addition, even less research is performed on the conversion from intravenous treatment to oral treatment for azoles in ASPs [18]. Therefore, the potential benefits of ASPs for antifungal agents should receive more attention. Additionally, the implementation of these antifungal stewardship programmes with the potential benefits should be assessed in clinical practice.

Another potential factor that can influence voriconazole pharmacokinetics is inflammation. During inflammation several drug-metabolising enzymes, including cytochrome P450 iso-enzymes, are down-regulated [19,20]. Since voriconazole is mainly metabolised by cytochrome P450 (CYP) iso-enzymes [6], its metabolism can be influenced during inflammation. In Chapter 5 we showed that the pharmacokinetics of voriconazole were indeed influenced in adult patients by severe inflammation, reflected by increased C-reactive protein (CRP) concentrations. During severe inflammation high and potentially toxic voriconazole concentrations

were observed, while trough concentrations decreased significantly if the infection and the degree of inflammation subsided, reflected by decreasing CRP concentrations. Based on the CYP2C19 genotype of the patient, the effect of inflammation was even more pronounced. For instance, the metabolism of voriconazole is more reduced during inflammation for intermediate metabolisers of CYP2C19 compared with extensive and ultra-rapid metabolisers of CYP2C19. Besides CYP2C19, voriconazole is also metabolised by CYP2C9 and CYP3A4, though to a lesser extent [6]. The metabolic capacity of CYP2C9 and CYP3A4 can also be reduced during inflammation [21,22]. In our study solely CYP2C19 genotyping was performed. A reduced metabolic capacity for CYP2C9 is also commonly observed in the Caucasian population [23]. Therefore, an intermediate metaboliser for both CYP2C19 and CYP2C9 can result in an even larger effect on voriconazole metabolism during inflammation. A recent study in 29 patients showed that the genetic score, including both CYP2C19 and CYP3A4 genotype, and inflammation significantly influenced voriconazole trough concentration [24]. By using the genetic score of a patient, where all CYP450 genotypes of interest are included, more information could be obtained on the metabolic capacity of the liver and the effect of inflammation on voriconazole metabolism. In this case, quantification of the main metabolite of a drug, active or not, gives important additional information on drug metabolism [10]. Overall, the effect of inflammation on voriconazole metabolism, including CYP2C19, CYP2C9 and CYP3A4 genotype should be studied for a better understanding of the variable voriconazole pharmacokinetics.

In children the effect of inflammation on voriconazole trough concentration is less pronounced compared to adults. In Chapter 6a we showed that in children aged  $\geq 12$  years, voriconazole trough concentrations are higher at elevated CRP concentrations ( $> 150$  mg/L). However, in children aged  $< 12$  years, a trend of increased voriconazole concentrations at a higher degree of inflammation was not observed. This could be explained by a higher metabolic capacity in children aged  $< 12$  years for voriconazole, confirmed by the linear pharmacokinetics of voriconazole in this patient group [25]. Yanni and colleagues showed that CYP2C19 activity was higher in children aged  $< 12$  years compared with adults, as well as flavin-containing mono-oxygenase (FMO) activity [26]. Although both CYP2C19 and FMO activity are reduced during inflammation [19], this does not seem to influence the metabolic capacity of the liver in children aged  $< 12$  years. For other drugs, including theophylline and midazolam, a reduced clearance was shown in children aged  $< 12$  years during inflammation [27]. However, these drugs are primarily metabolised by CYP1A2 and CYP3A4, which could explain the difference in drug clearance during inflammation. Since our study was based on retrospective data with a limited number of patients and a limited number of samples per patient a larger observational study should be performed including longitudinal data to gain more insight on the effect of inflammation in children from different age groups.

Based on the results of the studies described in Chapter 5 and 6a inflammatory parameters like CRP concentrations should be measured routinely in clinical practice during treatment with voriconazole for adults and possibly also in children aged 12 years or older. This results in a better understanding

of the variable voriconazole concentrations.

The synthesis of CRP is mainly regulated by the cytokine interleukin-6 (IL-6) [28]. Therefore, IL-6 concentrations can be an early predictor of inflammation resulting in a decreased metabolism of voriconazole and hence higher voriconazole trough concentrations. In a recently performed prospective study in adult haematology patients was shown that IL-6 concentrations were significantly correlated with voriconazole trough concentrations. However, the results of this study suggest that the IL-6 concentration is not a better predictor for the variable voriconazole trough concentrations than the CRP concentration [29]. Since CRP concentrations are more frequently measured in clinical practice and the costs are lower than measuring IL-6 concentrations, it is questionable whether measuring IL-6 concentrations provides more information on voriconazole metabolism during inflammation with acceptable costs. Since the sample size of this study was small and information on voriconazole metabolism was lacking, a larger prospective study should be performed with more frequent sampling of both inflammatory parameters and voriconazole and voriconazole-N-oxide concentration to confirm these findings.

## 8.2 Optimising voriconazole treatment

TDM is recommended in several guidelines [30,31], but it is questionable whether solely performing TDM is the ultimate solution to optimise and individualise treatment with voriconazole. In Chapter 6b we developed a pharmacokinetic/pharmacodynamic (PK/PD) mathematical model, where the circulating galactomannan concentration was used as pharmacodynamic parameter. Although the data included in this study are

sparse and should be confirmed by larger studies in which more patients are included, the results of this study suggests that the generally accepted therapeutic range of 1 – 6 mg/L<sup>[3]</sup> is not applicable for all patients treated with voriconazole and highlights the need for true individualised treatment with voriconazole. By performing TDM the variable pharmacokinetics of a patient is taken into account, but a factor to determine response to treatment is lacking. Especially for patients with a probable or proven fungal infection a biomarker to determine response to treatment should be included, like the galactomannan index. By combining the galactomannan index with the voriconazole concentration, a real-time indication is provided for the individual response of the patient to voriconazole treatment. Since this study was performed in paediatric patients, a similar study should be performed in adult patients. Subsequently this treatment strategy, including both pharmacokinetic and a derived pharmacodynamic parameter, should be applied in clinical practice to determine if this results in optimised voriconazole treatment.

TDM of voriconazole is recommended based on retrospective data<sup>[4,5]</sup> and limited prospective data<sup>[32,33]</sup>. Although it is currently uncertain if TDM guided treatment of voriconazole for adult patients with invasive aspergillosis is superior to the standard voriconazole dosing regimen, it is advised in international guidelines<sup>[30,31]</sup>. In Chapter 7 a multicentre, prospective, clinical trial was performed. In this study, it was shown that individualised voriconazole treatment by routinely using TDM in all adult patients with invasive aspergillosis was not superior compared with the standard dosing regimen of voriconazole without performing

TDM. Here, both response to treatment and patients for whom voriconazole treatment was discontinued due to an adverse event of voriconazole was included in the analysis. However, significantly more trough concentrations were found within the predefined therapeutic range for the TDM-group. The results of this study suggests that other factors, apart from TDM cause treatment failure of voriconazole. Therefore, the additional value of TDM must be further investigated, to determine which patients could benefit from TDM. For instance in patients with a more severe fungal infection (i.e. probable or proven infections) the benefits of TDM could be more pronounced compared with patients with a less severe fungal infection (e.g. a possible infection as compared to a probable or proven infection, or infections with a lower fungal load). Although we found no difference in response to treatment and adverse events resulting in voriconazole treatment discontinuation for patients with a more severe fungal infection, our study was not powered for this subgroup analysis. Therefore, these results should be confirmed or invalidated in a properly designed study with sufficient power.

Furthermore, emerging azole resistance is a global problem and the mortality rates are high in patients with documented azole resistant invasive aspergillosis<sup>[34,35]</sup>. Troke et al. suggested a trough concentration divided by the minimal inhibitory concentration (MIC) of 2 to 5 to optimise voriconazole treatment<sup>[33]</sup>. With the emerging problem of azole resistance, the probability of achieving adequate voriconazole exposure decreases with increasing MIC values. This also suggests that TDM could play an important role in less susceptible species, which should be

be confirmed in clinical practice. Again, this highlights the need for true individualised treatment of voriconazole, including not solely the voriconazole trough concentration if TDM is indicated, but both a pharmacokinetic and pharmacodynamic parameter, or other derived pharmacodynamic parameter with which response to treatment could be determined (i.e. galactomannan index). Additionally, this also highlights the importance of rapid molecular testing for the presence of mutants with reduced or lost susceptibility for triazoles to optimise treatment.

The impact and additional value of TDM for voriconazole could be highest during the initial and most critical phase of antifungal treatment. Although a therapeutic range of 1–6 mg/L is recommended for optimal treatment outcome and to avoid toxicity, it is unclear whether this therapeutic range should be maintained during the entire treatment with voriconazole, or solely in the initial phase. Therefore, more research should be performed to determine if TDM for voriconazole should be performed during the entire treatment with voriconazole, or solely during the initial and perhaps most critical phase of treatment. For patients with specific risk factors, for instance patients with persistent neutropenia, longer follow-up with TDM to optimise voriconazole treatment could have more additional value compared with patients who recover from neutropenia after one or two weeks. Patients who already failed on other antifungal treatment could also benefit from longer routinely use of TDM, because this is a more vulnerable population as well as patients with a fungal infection in for instance the central nervous system. Furthermore, patients receiving a strongly deviating voriconazole dose

should be followed up more often, because of the highly variable pharmacokinetics of this drug. Though, correct adjustment of the voriconazole dose remains difficult, because of the many different factors influencing voriconazole concentration as described earlier. Therefore, a proper dosing algorithm including multiple factors influencing voriconazole concentration, which is also easy to use in clinical practice should be developed.

Another important aspect in antifungal treatment is the financial burden for the health system. The ever continuous costs of antifungal treatment is a concern <sup>[36]</sup>. New antifungal drugs, such as isavuconazole, are available at higher costs compared to the generic variant of voriconazole. The efficacy of isavuconazole is comparable with voriconazole and antifungal susceptibility seems comparable. However, for isavuconazole less drug-related adverse events have been observed. In addition, the pharmacokinetics of voriconazole are highly variable as also shown in this thesis, while isavuconazole seems to have more predictable and linear pharmacokinetics with minimal inter-patient variability <sup>[37,38]</sup>. However, also with frequent use of TDM for voriconazole to maintain efficacy and avoid toxicity the treatment with voriconazole might be more cost-effective, compared with isavuconazole. Therefore, in future studies where different treatment strategies of antifungal agents are compared, cost-effectiveness should be included in the analysis to keep antifungal treatment affordable.

### 8.3 Final remarks

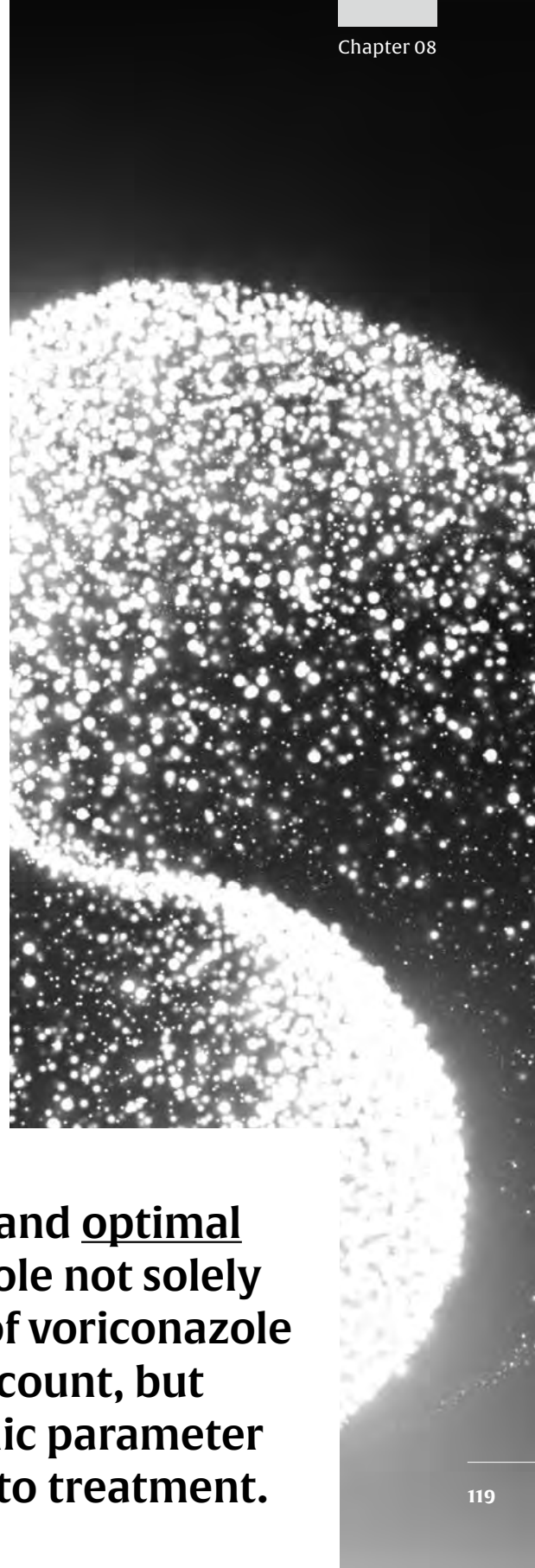
The number of patients at risk for invasive fungal infections is increasing <sup>[39]</sup>. Invasive aspergillosis is one of the most common



mould infections, for which voriconazole is recommended as first-line treatment [1,40]. However, it remains difficult to optimise treatment with voriconazole, because of the observed pharmacokinetic variability of this drug. In this thesis we have investigated which factors could influence the pharmacokinetic variability of voriconazole, including inflammation and bioavailability. We showed that inflammation contributes to the variable pharmacokinetics of voriconazole. In this thesis we have also shown that not solely the voriconazole trough concentration predicts treatment outcome. Other factors apart from the voriconazole trough concentration cause treatment failure as well. Therefore, to optimise treatment with voriconazole other factors, for instance the galactomannan index, could provide more information for optimal voriconazole treatment. In addition, although TDM is suggested to optimise treatment [30,31] the utility of TDM for voriconazole must be re-established in patients treated with voriconazole, to determine which patients could benefit the most from TDM. Last, more attention should be paid to the cost-effectiveness of the different treatment strategies of mould infections, because of the increasing costs of anti-fungal treatment.

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**For true individualised and optimal treatment of voriconazole not solely the pharmacokinetics of voriconazole should be taken into account, but also a pharmacodynamic parameter to determine response to treatment.**



## References

1. Oren I, Paul M. Up to date epidemiology, diagnosis and management of invasive fungal infections. *Clin Microbiol Infect* **2014** Jun;20 Suppl 6:1-4.
2. Blyth CC, Gilroy NM, Guy SD, Chambers ST, Cheong EY, Gottlieb T, et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, 2014. *Intern Med J* **2014** Dec;44(12b):1333-1349.
3. Luong ML, Al-Dabbagh M, Groll AH, Racil Z, Nannya Y, Mitsani D, et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. *J Antimicrob Chemother* **2016** Jul;71(7):1786-1799.
4. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrob Agents Chemother* **2012** Sep;56(9):4793-4799.
5. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis* **2008** Jan 15;46(2):201-211.
6. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* **2006**;45(7):649-663.
7. Wang G, Lei HP, Li Z, Tan ZR, Guo D, Fan L, et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers *Eur J Clin Pharmacol* **2009** Mar;65(3):281-285.
8. Lee S, Kim BH, Nam WS, Yoon SH, Cho JY, Shin SG, et al. Effect of CYP2C19 polymorphism on the pharmacokinetics of voriconazole after single and multiple doses in healthy volunteers *J Clin Pharmacol* **2012** Feb;52(2):195-203.
9. Bruggemann RJ, Alffenaar JW, Blijlevens NM, Billaud EM, Kosterink JG, Verweij PE, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. *Clin Infect Dis* **2009** May 15;48(10):1441-1458.
10. Veringa A, ter Avest M, Touw DJ, Alffenaar JC. Comment on: Utility of voriconazole therapeutic drug monitoring: a meta-analysis. *J Antimicrob Chemother* **2016**;doi:10.1093/jac/dkw284.
11. Roffey SJ, Cole S, Comby P, Gibson D, Jezequel SG, Nedderman AN, et al. The disposition of voriconazole in mouse, rat, rabbit, guinea pig, dog, and human. *Drug Metab Dispos* **2003** Jun;31(6):731-741.
12. Scholz I, Oberwittler H, Riedel KD, Burhenne J, Weiss J, Haefeli WE, et al. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype *Br J Clin Pharmacol* **2009** Dec;68(6):906-915.
13. Geist MJ, Egerer G, Burhenne J, Riedel KD, Weiss J, Mikus G. Steady-state pharmacokinetics and metabolism of voriconazole in patients. *J Antimicrob Chemother* **2013** Nov;68(11):2592-2599.
14. Han K, Capitano B, Bies R, Potoski BA, Husain S, Gilbert S, et al. Bioavailability and population pharmacokinetics of voriconazole in lung transplant recipients. *Antimicrob Agents Chemother* **2010** Oct;54(10):4424-4431.
15. Pascual A, Csajka C, Buclin T, Bolay S, Bille J, Calandra T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. *Clin Infect Dis* **2012** Aug;55(3):381-390.
16. Obach RS, Zhang QY, Dunbar D, Kaminsky LS. Metabolic characterization of the major human small intestinal cytochrome p450s. *Drug Metab Dispos* **2001** Mar;29(3):347-352.
17. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* **2016** May 15;62(10):e51-77.

18. Bienvenu AL, Argaud L, Aubrun F, Fellahi JL, Guerin C, Javouhey E, et al. A systematic review of interventions and performance measures for antifungal stewardship programmes. *J Antimicrob Chemother* **2018** Feb 1;73(2):297-305.
19. Aitken AE, Richardson TA, Morgan ET. Regulation of drug-metabolizing enzymes and transporters in inflammation. *Annu Rev Pharmacol Toxicol* **2006**;46:123-149.
20. Morgan ET. Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics *Clin Pharmacol Ther* **2009** Apr;85(4):434-438.
21. Aitken AE, Morgan ET. Gene-specific effects of inflammatory cytokines on cytochrome P450 2C, 2B6 and 3A4 mRNA levels in human hepatocytes. *Drug Metab Dispos* **2007** Sep;35(9):1687-1693.
22. Lee JI, Zhang L, Men AY, Kenna LA, Huang SM. CYP-mediated therapeutic protein-drug interactions: clinical findings, proposed mechanisms and regulatory implications. *Clin Pharmacokinet* **2010** May;49(5):295-310.
23. Xie HG, Prasad HC, Kim RB, Stein CM. CYP2C9 allelic variants: ethnic distribution and functional significance. *Adv Drug Deliv Rev* **2002** Nov 18;54(10):1257-1270.
24. Gautier-Veyret E, Bailly S, Fonrose X, Tonini J, Chevalier S, Thiebaut-Bertrand A, et al. Pharmacogenetics may influence the impact of inflammation on voriconazole trough concentrations. *Pharmacogenomics* **2017** Aug;18(12):1119-1123.
25. Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. *Antimicrob Agents Chemother* **2009** Mar;53(3):935-944.
26. Yanni SB, Annaert PP, Augustijns P, Ibrahim JG, Benjamin DK, Jr, Thakker DR. In vitro hepatic metabolism explains higher clearance of voriconazole in children versus adults: role of CYP2C19 and flavin-containing monooxygenase 3. *Drug Metab Dispos* **2010** Jan;38(1):25-31.
27. Vet NJ, Brussee JM, de Hoog M, Mooij MG, Verlaat CW, Jerchel IS, et al. Inflammation and Organ Failure Severely Affect Midazolam Clearance in Critically Ill Children *Am J Respir Crit Care Med* **2016** Jan 21.
28. Ansar W, Ghosh S. C-reactive protein and the biology of disease. *Immunol Res* **2013** May;56(1):131-142.
29. Vreugdenhil B, van der Velden WJFM, Feuth T, Kox M, Pickkers P, van de Veerdonk FL, et al. Moderate correlation between systemic IL-6 responses and CRP with trough concentrations of voriconazole. *Br J Clin Pharmacol* **2018** May 9.
30. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother* **2014** May;69(5):1162-1176.
31. Chau MM, Kong DC, van Hal SJ, Urbancic K, Trubiano JA, Cassumbhoy M, et al. Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy, **2014**. *Intern Med J* 2014 Dec;44(12b):1364-1388.
32. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. *J Clin Pharmacol* **2006** Feb;46(2):235-243.
33. Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. *Antimicrob Agents Chemother* **2011** Oct;55(10):4782-4788.
34. Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole Resistance in *Aspergillus fumigatus*: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles? *Clin Infect Dis* **2016** Feb 1;62(3):362-368.

35. Verweij PE, Lestrade PP, Melchers WJ, Meis JF. Azole resistance surveillance in *Aspergillus fumigatus*: beneficial or biased? *J Antimicrob Chemother* **2016** Aug;71(8):2079-2082.
36. Taylor P. Antifungal Drugs: Technologies and Global Markets. March 2017; June **2018**, available at: <https://www.bccresearch.com/market-research/pharmaceuticals/antifungal-drugs-markets-report-phm029f.html>.
37. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet* **2016** Feb 20;387(10020):760-769.
38. Buil JB, Bruggemann RJM, Wasmann RE, Zoll J, Meis JF, Melchers WJG, et al. Isavuconazole susceptibility of clinical *Aspergillus fumigatus* isolates and feasibility of isavuconazole dose escalation to treat isolates with elevated MICs. *J Antimicrob Chemother* **2018** Jan 1;73(1):134-142.
39. Perfect JR. The antifungal pipeline: a reality check. *Nat Rev Drug Discov* **2017** May 12.
40. Patterson TF, Thompson GR, 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* **2016** Aug 15;63(4):e1-e60.

