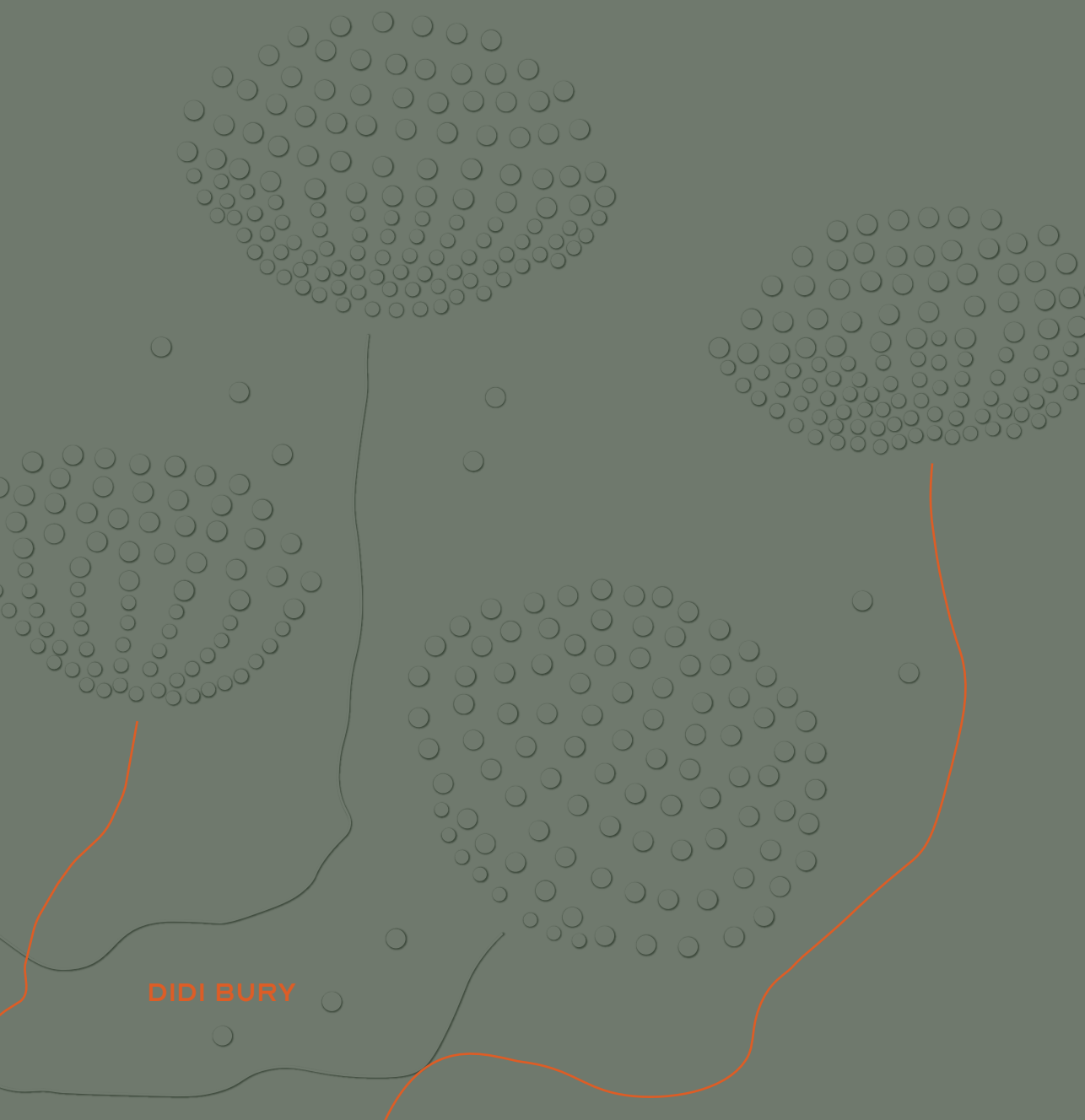
BROADENING MOULD-ACTIVE STRATEGIES IN PAEDIATRIC HAEMATO-ONCOLOGY PATIENTS



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Broadening mould-active strategies in paediatric haemato-oncology patients

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Broadening mould-active strategies in paediatric haemato-oncology patients

Verbreden van antischimmel strategieën bij pediatrische hemato-oncologische patiënten

(met een samenvatting in het Nederlands)

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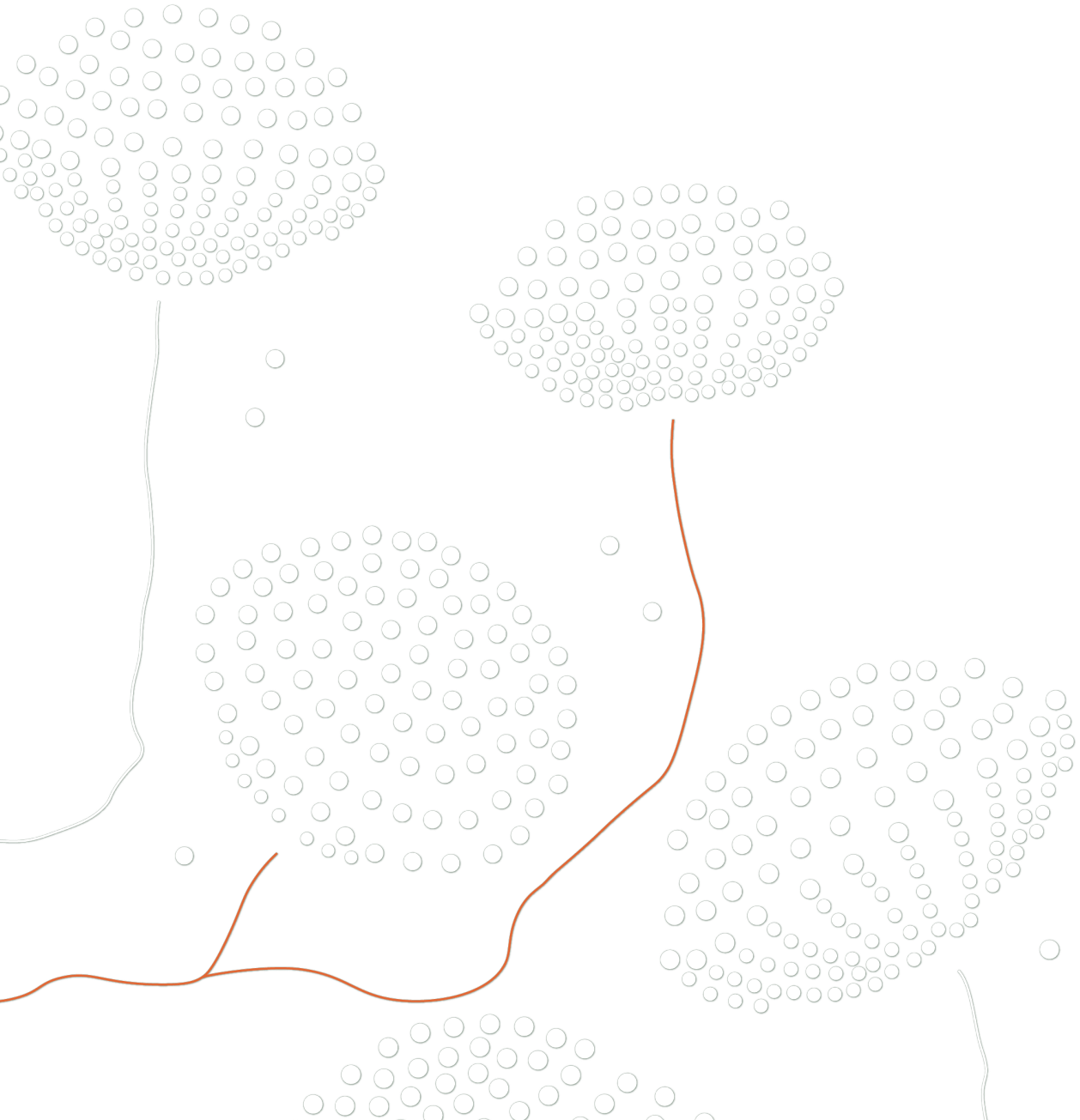
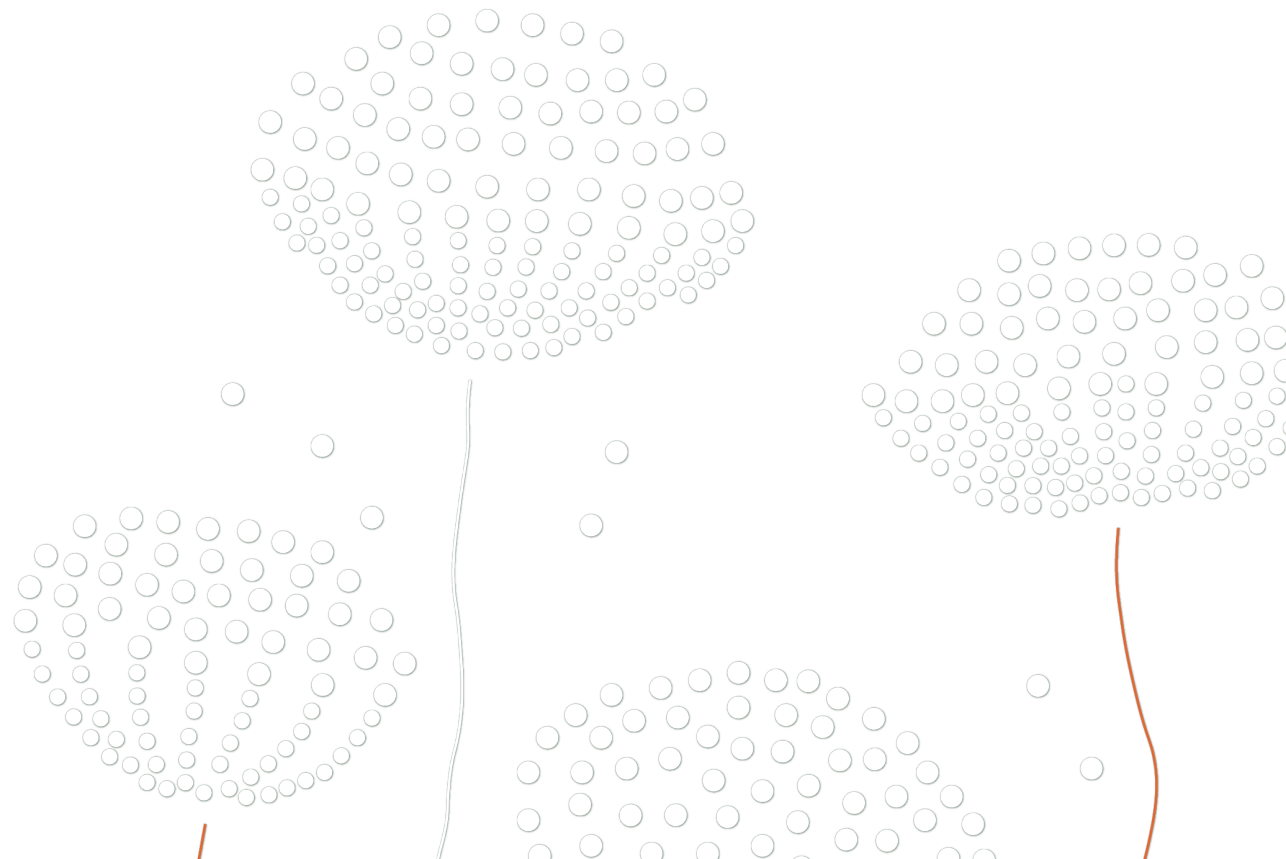
Content

CHAPTER 1



GENERAL INTRODUCTION



Paediatric haemato-oncology patients

Paediatric haemato-oncology enfolds all aspects of blood cancer in children and covers the treatment of different types of leukaemia, myeloproliferative diseases, lymphomas, histiocytosis, and bone marrow failure syndromes.

Despite the advances in the haemato-oncological treatment and associated disease outcome, treatment-related mortality (TRM) remains a concern. In the Dutch paediatric haemato-oncology population, TRM occurred in around 9% of the patients in the first five years after diagnosis. Infectious diseases are responsible for nearly half of these treatment-related deaths.[1] Specifically, children and adolescents receiving intensive myelosuppressive chemotherapy for acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), those with relapsed disease as well as paediatric hematopoietic stem-cell transplantation (HSCT) recipients are at risk for infections and therefore as well for TRM. The susceptibility to infection is most likely a result of high-dose glucocorticoids and aggressive chemotherapy, causing treatment-induced severe neutropenia and inhibition of the immune response.[1] The pathogens causing infection-related mortality are predominantly bacteria, followed by fungi and viruses.[2] Specifically, the morbidity and mortality associated with invasive fungal disease (IFD) are considerable. IFD could potentially lead to substantial implications for cancer treatment, such as delays in cancer treatment, and negatively impact the quality of life of paediatric patients.

The incidence rates of IFD differ among paediatric haemato-oncology populations. AML patients and HSCT recipients carry the highest relative risk for IFD.[3] However, ALL is the most prevalent type of cancer in children with around 110 patients each year in The Netherlands and the highest absolute number of patients with IFD originates from this group. Globally, incidence rates of IFD in paediatric patients with ALL are as high as 2-35% depending on the geographical location, treatment strategy, and the use of preventive strategies.(4-9) IFD primarily occurs during the early phases of treatment of ALL.[4, 5] Known risk factors for IFD include age (≥12 years), high white blood cell count at diagnosis[6] and the absence of antifungal prophylaxis. In the Netherlands, the incidence rate for IFD is around 8% during the ALL-11 treatment protocol [Data on file Dutch Childhood Oncology Group (DCOG)]. This results in an absolute number of 8-9 paediatric patients with ALL that are diagnosed with IFD every year in The Netherlands. The overall 1-year mortality rate for IFD in a comparable AIEOP-BFM ALL 2009 cohort was 12.1%.[6]

Invasive fungal disease

Fungal infections mainly occur during the induction, consolidation, and delayed intensification courses of treatment.[6, 7] The primary pathogens responsible for these

infections in ALL patients are yeasts, such as *Candida* spp., and filamentous moulds, such as *Aspergillus* spp*.* Other less common filamentous moulds that can cause IFD are *Mucorales* spp., *Fusarium* spp., *Alternaria* spp., and *Scedosporium* spp.[3] While all yeasts as well as moulds pose serious complications in paediatric patients with ALL, this thesis has a particular emphasize on invasive *Aspergillus* infections as the most dominant fungal infection in this population.

The majority of IMD in paediatric patients with ALL in The Netherlands is caused by *Aspergillus* species. While the abovementioned incidence for IFD in general is around 8%, the estimated incidence for specifically *Aspergillus* infections is around 6-7% [data on file, Dutch Childhood Oncology Group (DCOG)]. Although not extensively described, internationally the incidence of *Aspergillus* infections in paediatric patients with ALL specifically is estimated at 0.6 – 5%.[8-13] The incidence of *Aspergillus* infections in our population thus seems to be somewhat above the upper limit that was previously reported.

Knowledge on local epidemiology of *Aspergillus* and *non-Aspergillus* infections and details on the time course of occurrence of these episodes in paediatric haemato-oncology patients is necessary to establish the most appropriate diagnostic and treatment strategies, including choices for prophylaxis, empirical and diagnostic-driven strategies.

Mould-active strategies

Four different antifungal strategies can be distinguished for IMD[14]:

- *Prophylaxis* refers to the preventive strategy of administering mould-active agents in at-risk patient populations without clinical signs and symptoms.
- *Empirical strategy* refers to the start of mould-active agents in at-risk paediatric patients and in the presence of (aspecific) clinical signs and symptoms.
- *Pre-emptive strategy* refers to the diagnostics-driven start of mould-active agents.
- *Targeted strategy* refers to the start of specific mould-active agents in the presence of a documented fungal pathogen.

The disadvantage of the first two strategies is the high number needed to “treat to prevent” or treat an IMD during their haematological treatment course. Consequences of overuse may include the risk of increased toxicity and costs.[15] However, prophylactic strategies are justified during at risk treatment courses for paediatric cancer patients when fungal infections typically exceed 5%.[16] The empirical strategy and the pre-

emptive strategy seem to be equally effective, but the pre-emptive strategy significantly decreases the use of antifungal agents but requires intensive diagnostic procedures to early detect a fungal infection.[15, 17] In the Dutch protocol for childhood ALL treatment a pre-emptive strategy for IMD management has been implemented during the at-risk induction course. This strategy was preferred due to drug-drug interactions with the combination of the chemotherapeutic agent vincristine and triazoles during this course and the lack of a suitable alternative prophylactic strategy. During other at-risk treatment courses prophylaxis with itraconazole was administered. To provide suitable mould-active prophylaxis during the early stage of treatment, it is important to explore alternative strategies that I) are generally well tolerated, II) ideally without significant drug-drug interactions with the current chemotherapeutic agents used, and III) that do not exceedingly affect the treatment costs. The present targeted strategy for IMD during ALL treatment in children involves initial combination therapy due to relatively high azole resistance frequencies in The Netherlands[18], and in the absence of documented azole resistance, serving as a bridge until therapeutic azole concentration are achieved.

Mould-active agents

The prophylaxis and treatment of IMD, and specifically *Aspergillus* infections, rely on three classes of mould-active agents : I) triazoles (isavuconazole, itraconazole, posaconazole, voriconazole), II) polyenes (amphotericin B and its lipid formulations), and III) echinocandins (anidulafungin, caspofungin, micafungin). This thesis focuses on the classes of triazoles and echinocandins. In Table 1 the mould-active agents with activity against *Aspergillus* spp. for use in paediatric patients are summarized. Within the classes of triazoles and echinocandins, only posaconazole, voriconazole and caspofungin are licensed for *Aspergillus* infection in paediatric patients.[19-24] Itraconazole, isavuconazole, anidulafungin and micafungin have not been investigated for either paediatric patients and/or for the purpose of obtaining this label indication. Therefore, off-label use of these agents is common for specific age groups or indications that are not (yet) approved by regulatory agencies

Table 1 Antifungal dosage forms and recommended dosing regimens for paediatric use.

Mould-active agent	Formulation		Prophylaxis/ treatment	Loading dose	Maintenance dose	Label and/ or guideline recommendation	Ref.
Triazoles							
Isavuconazole*	oral capsule / intravenous		Prophylaxis/ treatment	5.4 mg/kg/dose isavuconazole (max. 200 mg) three times daily on day 1 and 2	5.4 mg/kg/dose isavuconazole (max. 200 mg) once daily	None, study results from pharmaceutical company	25
Itraconazole*	oral capsule / oral suspension# / (intravenous)		Prophylaxis	Not recommended	2.5 mg/kg/dose twice daily (oral suspension)	Guideline recommendation	26
			Treatment	5 mg/kg/dose twice daily on day 1 (oral suspension)	2.5 mg/kg/dose twice daily (oral suspension)		
Posaconazole	Oral suspension		Prophylaxis[&]	200 mg three times daily	200 mg three times daily	FDA, EMA	19, 20
	Oral tablet#		Prophylaxis[+]/ treatment[~]	300 mg twice daily on day 1	300 mg once daily		
	Oral powder and solvent for oral suspension (delayed release)	10-<12 kg	Prophylaxis[±]/ treatment[%±]	90 twice daily on day 1	90 once daily		
		13-<17 kg		120 twice daily on day 1	120 once daily		
		17-<21 kg		150 twice daily on day 1	150 once daily		
		21-<26 kg		180 twice daily on day 1	180 once daily		
		26-<36 kg		210 twice daily on day 1	210 once daily		
		36-40 kg		240 twice daily on day 1	240 once daily		
	Intravenous		Prophylaxis[±]	6 mg/kg (max. 300 mg) twice daily on day 1	6 mg/kg (max. 300 mg) once daily		
			Treatment[~]	300 mg twice daily on day 1	300 mg once daily		

Table 1 Continued

Mould-active agent	Formulation		Prophylaxis/ treatment	Loading dose	Maintenance dose	Label and/ or guideline recommendation	Ref.
Voriconazole	Oral tablet/ Suspension	2–11 years or aged 12–14 years (<50 kg)	Prophylaxis^/ treatment	Not recommended	9 mg/kg (max. 350 mg) twice daily	FDA, EMA, guideline recommendation	21, 22, 26
		12–14 years (≥50 kg) or aged ≥14–15 years	Prophylaxis^/ Treatment	200-400 mg twice daily on day 1	100-200 mg twice daily		
	Intravenous	2–11 years or aged 12–14 years (<50 kg)	Prophylaxis^/ treatment	9 mg/kg twice daily on day 1	8 mg/kg twice daily		
		12–14 years (≥50 kg) or aged ≥14–15 years	Prophylaxis^/ treatment	6 mg/kg twice daily on day 1	4 mg/kg twice daily		
Echinocandins							
Anidulafungin*	Intravenous		-	-	-	None	-
Caspofungin	Intravenous	<3 months	Treatment	-	25 mg/m^2	guideline recommendation	26
		3 -12 months	Treatment	-	50 mg/m^2	guideline recommendation	26
		12 months – 17 years	Empirical therapy/ treatment	70 mg/m^2 (max. 70 mg)	50 mg/m^2 (max. 70 mg)	EMA, guideline recommendation	24, 26
		<3 months – 17 years	Empirical therapy/ treatment	70 mg/m^2 (max. 70 mg)	50 mg/m^2 (max. 70 mg)	FDA	23
Micafungin*	Intravenous		Prophylaxis	-	1 mg/kg (max. 50 mg)	Guideline recommendation	26
			Treatment	-	2-4 mg/kg (max. 200 mg)		

Table 1 Continued

Abbreviations: FDA = U.S. Food & Drug administration; EMA = European Medicines Agency
**Not approved in patients <18 years of age.*
#Preferred formulation
&Licensed in patients ≥13 years of age (USA), and not approved in patients <18 years of age (Europe).
+Licensed in patients ≥2 years of age and ≥40 kg.
~Licensed in patients ≥13 years of age (USA) and in patients ≥2 years of age and ≥40 kg (Europe).
±Licensed in patients ≥2 years of age.
%Licensed for treatment of invasive fungal disease in patients ≥2 years of age (Europe).
^Licensed for prophylaxis of invasive fungal disease in patients ≥2 years of age (Europe).

Pharmacology of triazoles and echinocandins

Triazoles are inhibitors of the enzyme lanosterol 14α-demethylase (cytochrome P450 [CYP] 51) and block the production of ergosterol, an essential component of the fungal cell membrane. Without ergosterol and with the accumulation of its toxic sterol precursors, this results in a weakened and dysfunctional fungal cell membrane.[19-22, 27-29]

Triazoles are available in both oral and intravenous formulations as depicted in Table 1. Itraconazole, posaconazole and voriconazole are available as liquid oral formulations, solid oral formulations (tablets) or intravenous formulations.[19-22, 29] Isavuconazole is available in a solid oral formulation (capsule) and intravenous formulation.[27, 28] The liquid oral formulation is the preferred formulation for itraconazole and the solid oral formulation is the preferred formulation for posaconazole given the improved bioavailability of these products. The availability of oral formulations is beneficial for step-down therapy after intravenous therapy and offers a more patient friendly regimens for outpatient treatment courses.

Unlike triazoles, echinocandins inhibit the glucan synthase enzyme and thereby block the synthesis of an essential component of the fungal cell wall, 1,3-β-D-glucan. This causes characteristic changes and dysfunction of the fungal cell wall.[23, 24, 30-33]

Echinocandins are only available as intravenous formulations.[23, 24, 30-33] Therefore, their daily dosing regimen is an invasive strategy for paediatric patients, especially during outpatient treatment courses.

Anti-mould spectrum

Each class of antifungal agent affects the fungal cell differently. Even within their class, each antifungal agent has a different antifungal spectrum. An overview of the anti-mould activity of triazoles and echinocandins is given in Table 2 and 3, respectively.[18]

Table 2. Anti-mould spectrum triazoles. Adapted with permission from.[18]

Species	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Aspergillus	S/r	S/r	S/r	S/r
Mucorales	S/r	R	S/r	R

S = sensitive, R = resistant, S/r = majority sensitive/minority resistant

Table 3. Anti-mould spectrum echinocandins.[18]

Species	Anidulafungin	Caspofungin	Micafungin
Aspergillus	S/r	S/r	S/r
Mucorales	R	R	R

R = resistant, S/r = majority sensitive/minority resistant

Drug-drug Interactions

Not only the fungal CYP enzyme system, but also the human equivalent of the CYP enzyme system is affected by triazoles. Triazoles are in varying degrees substrates and/or inhibitors of this system and are therefore notorious for their variety of drug-drug interactions.[23, 24, 30-33] Important in the paediatric haemato-oncological population are the interactions with chemotherapeutic agents.[34] For instance, first-line prophylactic and treatment options with triazoles are limited during specific courses where patients are at risk for invasive *Aspergillus* infections, because they receive vincristine as part of their cancer treatment. Combination of a triazole drug with vincristine causes unwanted and serious side effects due to toxic vincristine exposures. Exploring (non-)triazole prophylactic regimens as mould-active prophylaxis that lack or have a less pronounced interaction with vincristine, might be beneficial for prophylaxis during these courses.

As the target of echinocandins is fungi-specific, relatively few clinically relevant drug-drug interactions are expected with the use of echinocandins.[23, 24, 30-33]. Given their favourable interaction profile, they are a meaningful class of antifungal agents to further investigate for alternative antifungal strategies, such as prophylaxis for *Aspergillus* infections.

While various antifungal agents are available for the prophylaxis and treatment of IMD, defining safe and effective dosing strategies remain a challenge in paediatric populations. Understanding the pharmacokinetics and the associated processes (i.e. absorption, distribution, metabolism, and excretion) of mould-active agents in paediatric haematology patients is required to develop and optimize antifungal strategies. Pharmacokinetic modelling is an insightful tool to determine drug pharmacokinetics on a population level. Next to this pharmacokinetic knowledge, expected drug exposures can be determined for antifungal agents via simulation following varying dosing regimens. These analyses may include assessing existing dosing strategies to achieve the intended drug exposure, or ascertain the expected exposure of new dosages and strategies.

The scarcity of pharmacokinetic data in paediatric cancer patients to guide optimal dosing of mould-active agents (i.e. isavuconazole and micafungin) highlights the importance of addressing these topics for better management of IMD.

Scope of this thesis

The incidence and mortality rates of IMD in paediatric haemato-oncology patients remain relatively high, whereas mould-active prophylactic and treatment options continue to be limited and IMD management remains challenging. In addition, various aspects necessary for optimal management of IMD in paediatric populations are not yet recognized. The

knowledge gaps discussed in this thesis are described in Table 4. In this thesis, we aim to better understand and broaden mould-active strategies for the prophylaxis and treatment of IMD in paediatric patients. Three major sections are addressed, as outlined in Table 4. Section I of this thesis describes the clinical presentation and outcome of IMD in paediatric patients with ALL (**Chapter 2**). Section II of this thesis examines the pharmacokinetics of different mould-active agents in paediatric patients (**Chapter 3, 4 and 5**). Section III of this thesis evaluates the efficacy of micafungin for prophylaxis of invasive *Aspergillus* infections in an alternative dosing regimen (**Chapter 6**).

The concluding **chapter (7)** considers the general discussion and perspectives, and addresses directions for future research on broadening antifungal strategies in paediatric populations.

Table 4. Knowledge gaps and scopes of this thesis

Section	Knowledge gaps	Chapter	Aim of the study
I	An (up-to-date) overview of IMD in paediatric patients with ALL in The Netherlands	2	Description of the presentation, diagnostic work-up, treatment and outcome of invasive mould infections in Dutch paediatric patients with ALL
II	Pharmacokinetics of antifungal agents in paediatric patient populations	3	Provide an up-to-date review of the literature on pharmacokinetic data of triazoles in paediatric patient populations
		4	Assessment of the pharmacokinetics of isavuconazole in Dutch paediatric cancer patients
		5	Assessment of the pharmacokinetics of a twice-a-week micafungin regimen in Dutch paediatric patients with ALL
III	Efficacy of alternative dosing strategies for mould-active prophylaxis in paediatric oncology patients	6	Evaluation of the efficacy of a twice-a-week micafungin regimen for *Aspergillus* prophylaxis in Dutch paediatric patients with ALL

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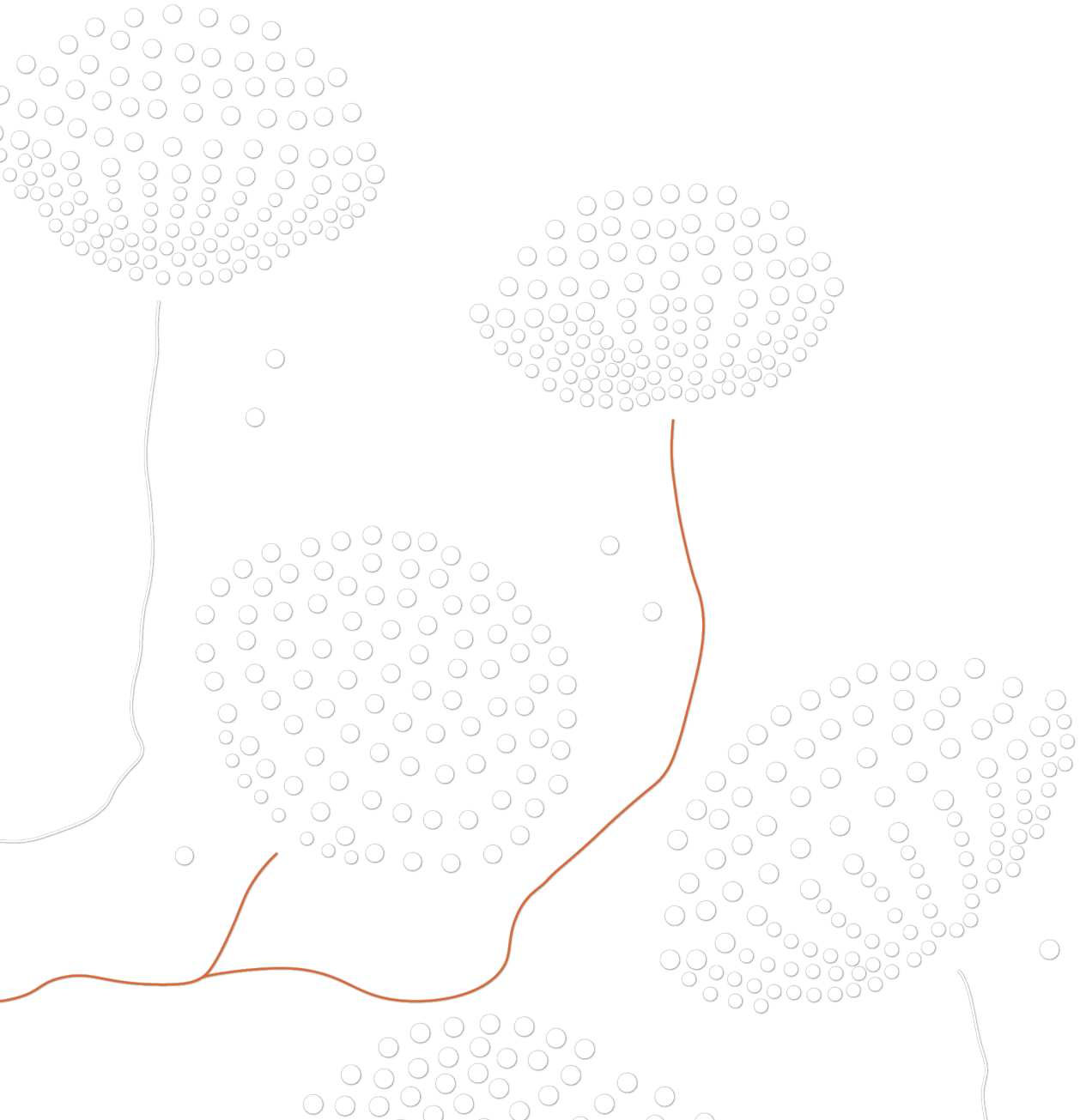
CHAPTER 2



CLINICAL PRESENTATION AND OUTCOME OF INVASIVE MOULD DISEASE IN PAEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

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**shared first authorship*

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Abstract

Objectives

Childhood acute lymphoblastic leukaemia (ALL) cure rates have improved, but invasive mould disease (IMD) remains a life-threatening complication. Here, we evaluate the epidemiology, clinical presentation, treatment and outcome of IMD in paediatric patients with ALL.

Methods

Patients (1-18 years) treated according to the Dutch Childhood Oncology Group (DCOG) ALL-11 protocol from 2012-2021 were analysed for probable and proven IMD. Data was extracted from the Dutch national registry and the electronic health care system.

Results

Among 643 patients with ALL, 47 (7.3%) were diagnosed with a probable (n=29) or proven (n=18) IMD. Aspergillosis was diagnosed in 42 (89%) patients. Forty-one episodes (87%) occurred during the induction (n=20) and first consolidation (n=21) course. The median age at ALL diagnosis was 5 years [IQR 3-10] in the overall group versus 14 years [IQR 7-16] in the IMD group. Two-third of the patients did not receive mould-active prophylaxis. The most prevalent clinical symptoms at presentation were persistent fever and respiratory symptoms. The lungs were the most common site of infection with involvement in 44 (94%) patients, followed by the CNS in 16 (34%) patients. The 6-week and 12-week mortality rate after IMD diagnosis was 10.6% and 14.9%, respectively.

Conclusions

In our paediatric cohort a notable incidence of probable and proven IMD was observed during the early stages of treatment. Remarkable is the high frequency of CNS involvement. These findings highlight the importance of effective prophylactic strategies and warrant early brain imaging.

Introduction

Acute lymphoblastic leukaemia (ALL) has shown significant progress with respect to the 5-year survival rate, exceeding 90% for paediatric patients. Despite this progress in survival rate, a portion of patients still face challenges in attaining complete cure, due to incurable relapses and toxic deaths.[1] Among the various causes of death, infectious diseases, including invasive mould disease (IMD), have emerged as a leading factor.[2, 3]

IMD primarily arises due to a weakened immune response. Since the administration of chemotherapy to children with ALL severely compromises their immune system during parts of their treatment, they are at-risk for developing IMD. The reported incidence rates of IMD in children with ALL vary from 0.5-7.1 % worldwide and depend on factors such as the treatment protocol, the use of mould-active prophylaxis and the geographical area.[4-9]

Despite its significance, research focusing on the epidemiology, clinical features, treatment, and outcome of IMD in children with ALL is limited. However, comprehending the epidemiology of IMD throughout the entire treatment protocol is crucial for identifying high-risk treatment courses and determining the potential benefits of mould-active treatment strategies, including prophylaxis and diagnostic-driven strategies. Moreover, recognising the clinical signs and symptoms during the initial presentation of IMD is essential for early diagnosis and timely initiation of mould-active treatment. Consequently, there is a need for a better understanding of the clinical aspects of IMD to enhance its management and outcomes.

In this study, we evaluate the incidence and describe the clinical signs and symptoms at initial presentation, treatment and outcome of IMD in paediatric patients treated according to the Dutch Childhood Oncology Group (DCOG) ALL-11 protocol from 2012-2021.

Methods

This study was a national multi-centre, retrospective cohort study on incidence, clinical presentation, treatment and outcome of IMD in children with ALL. The study population consisted of all newly diagnosed patients with ALL in the Netherlands, who started treatment according to the DCOG ALL-11 protocol between April 2012 and August 2018.[10] The follow-up period extended until the end of ALL treatment up to June 2021. Patients were treated in the following centres in The Netherlands: Princess Máxima Center for Pediatric Oncology (Utrecht), Wilhelmina Children's Hospital (Utrecht), Radboud university medical center (Nijmegen), Erasmus Medical Center (Rotterdam),

VU University Medical Center (Amsterdam), Amsterdam Medical Center (Amsterdam), Academic Hospital Maastricht (Maastricht), Leiden University Medical Center (Leiden) and University Medical Center Groningen (Groningen).

All patients underwent a diagnostic-driven approach with once weekly, and if feasible twice weekly, serum galactomannan screening during the induction course (week 0-5) and first consolidation course (week 6-10). Triazole prophylaxis was withheld during the induction course due to weekly vincristine use and the relevant drug interactions. Subsequently, children received mould-active prophylaxis with itraconazole during their first consolidation course. Therapeutic drug monitoring (TDM) was only routinely performed for itraconazole in a limited number of centres. After risk stratification for their ALL treatment, the protocol for mould-active prophylaxis is different for the three risk groups for ALL treatment (SRG, MRG and HRG). The standard risk group (SRG) received no mould-active prophylaxis beyond first consolidation. The medium risk group (MRG) received mould-active prophylaxis during the first 12 weeks of maintenance treatment for those who got doxorubicin. The high risk group (HRG) received mould-active prophylaxis during their HRG blocks and re-induction therapy. During HRG blocks and re-induction therapy, serum galactomannan was screened once weekly, and if feasible twice weekly.

In case of repeated positive serum galactomannan or persistent fever (>96 hours) in neutropenia while receiving broad-spectrum antibiotics, the following diagnostics were performed according to the protocol: High-Resolution Computed Tomography (HRCT) thorax, and if not recently performed, serum galactomannan. In case of an abnormal HRCT thorax suggestive of pulmonary fungal infection, further diagnostics (bronchoalveolar lavage, biopsy on indication) were performed. Magnetic Resonance Imaging (MRI) of the cerebrum/sinuses was performed based on the discretion of the centre-specific physicians. In case of a positive MRI, if feasible, cerebrospinal fluid analysis and/or biopsy of the lesion were performed. The standard antifungal treatment for a suspected pulmonary and/or cerebral IMD in children with ALL was voriconazole in combination with liposomal amphotericin B. Protocol deviations were possible at the discretion of the treating physician. In the absence of documented azole resistance and when stable voriconazole trough levels were reached, treatment was switched to voriconazole monotherapy. TDM was routinely performed in patients receiving voriconazole.

All Serious Adverse Events and toxicity adverse events were prospectively registered as part of the national registry of the DCOG, including systemic or invasive fungal infections. The following variables were obtained from the DCOG ALL-11 database and the electronic health care system (EHRS): demographics (age, sex, immunophenotype

and genotype of ALL), disease characteristics (duration of ALL treatment until (suspected) IMD, treatment phase, use of mould-active agents, classification and characteristics of the IMD episode (clinical manifestations at presentation, galactomannan values, species, resistance analyses, involved sites, treatment and outcome).

Definitions

Proven and probable mould infections were defined according to the European Organization for Research and Treatment in Cancer/Mycoses Study Group 2008 (EORTC/MSG) criteria.[11] Categorisation of IMD was conducted independently by two researchers (DB and TW) using the EORTC/MSG criteria.

Statistical analysis

Descriptive statistics were presented as the median and interquartile ranges (IQR) for continuous data and frequencies and percentages for categorical data. For baseline characteristics, the Mann-Whitney U test was used to compare continuous data and the Pearson's chi-square test or Fisher's exact test were used to compare categorical data between between patients with and without mould infection.

Ethics

All patients provided written informed consent for the DCOG ALL-11 protocol, including studies on its side effects. The study protocol was approved by and the Medical Ethics Assessment Committee Utrecht (19-163/C).

Results

643 children with newly diagnosed with ALL were included in this study. Forty-seven (7.3%) patients developed a probable or proven IMD. A total of 29 probable (62%) and 18 proven (38%) IMD episodes were categorized according to the EORTC criteria. The median age at ALL diagnosis was 5 years [IQR 3-9], and 39% was female in the non-IMD group versus 14 years [IQR 7-16; p=.000], and 57% (p=.014) in the IMD group. The baseline characteristics are presented in Table 1. In 42 out of 47 episodes (89%) aspergillosis was diagnosed, with an identified pathogen in 23 patients. *Aspergillus fumigatus* being the most commonly identified pathogen in 19 of the 23 patients. In one patient a mixed infection with *Aspergillus*, *Fusarium* and *Alternaria* was documented. Resistance analysis was performed in 19 isolates from 23 patients, and voriconazole resistance (MIC $\geq$ 1.0 mg/L) of *Aspergillus* isolates was found in four out of 19 isolates

(21%), *Mucorales* spp. were isolated in three patients (6%), and *Alternaria* spp. in two patients (4%). A detailed overview is given in Table 2.

Table 1. Demographic characteristics

Number of patients, N (%)	Overall group	Non-IMD group	IMD group	p-value
	643 (100)	596 (92.7)	47 (7.3)	
Median age at ALL diagnosis, years (IQR)	5 (3-10)	5 (3-9)	14 (7-16)	.000[a]
Sex, N (%)				
Male	383 (59.6)	363 (60.1)	20(42.6)	.014[b]
Female	260 (40.4)	233 (39.1)	27(57.4)	
Type of ALL, N (%)				
Pro-B ALL	13 (2.0)	10 (1.7)	3 (6.4)	.075[c]
c-ALL	364 (56.6)	334 (56.0)	30 (63.8)	
Pre-B ALL	174 (27.1)	166 (27.9)	8 (17.0)	
T-ALL	92 (14.3)	86 (14.4)	6 (12.8)	
Genetic variation, N (%)				
Down syndrome	17 (2.6)	17 (2.9)	0 (0)	.627[c]

Abbreviations: IMD = invasive mould disease; ALL = acute lymphoblastic leukaemia; pro-B ALL = precursor B acute lymphoblastic leukaemia with no expression of CD10; c-ALL = common acute lymphoblastic leukaemia; Pre-B ALL = precursor B-lineage acute lymphoblastic leukaemia; T-ALL= T-lineage acute lymphoblastic leukaemia.
[a]Mann-Whitney U Test.
[b]Pearson's Chi-Square Test.
[c]Fisher's exact test.

Table 2. EORTC/MSG classification

	EORTC/MSG classification	
	Proven *N (sample type)*	**Probable *N***
Number of invasive mould disease	17	30
Species		
Aspergillus		
A. fumigatus	10 (liquor n=1, biopsy n=7, pleural fluid n=1, abscess n=1)	9[$]
A. flavus	1 (biopsy)	1
A. nidulans	1 (biopsy)	
A. terreus	1 (biopsy)	
Not further specified^	1 (puncture)	18[#]
Mucorales		
Lichtheimia corymbifera	1 (biopsy)	
Cunninghamella bertholletiae	1 (biopsy)	
Not further specified~	1 (biopsy)	
Alternaria		2*

^based on positive GM and/or positive *Aspergillus* PCR and/or histology typical for *Aspergillus*.
[$]1x positive PCR for *Aspergillus* fumigatus and *Aspergillus* versicolor. 1x mixed infection with *Fusarium* and *Alternaria.*
[#]2x positive culture for *Penicillium* nalgiovense.
~based on histology typical for *Mucorales* in BAL fluid and lung biopsy.
*1x mixed infection with *Trichophyton* rubrum.

Disease characteristics

Forty-one out of 47 episodes (87%) occurred during the induction (n=20, 42.6%) and first consolidation (n=21, 44.7%) course. The median duration of ALL treatment until the diagnosis of an IMD episode was 42 days (IQR 33-70). Prior to the presentation of an IMD, no mould-active prophylaxis was administered in the protocol course preceding IMD diagnosis in 32 out of 47 episodes (68%).

In 45 out of the 47 patients with IMD (96%) serum galactomannan was routinely screened. In only two of these patients , a positive galactomannan result was the only indication for further diagnostic work-up. In another three patients, a positive galactomannan result was observed among other clinical symptoms that were associated with a different condition. In these three patients the positive galactomannan result triggered further diagnostic work-up regarding IMD. In another 10 of the 45 patients, positive galactomannan results were observed at any time during the course of the IMD. Serum galactomannan remained negative in 30 patients, including the three patients with a *Mucorales* infection and one with an *Alternaria* infection.

The clinical symptoms at presentation are described in Table 3. In 29 out of 47 episodes (62%), patients presented with persistent fever, in the majority of these episodes during neutropenia (n=27). In seven of these 29 episodes fever was the single clinical symptom at presentation. Respiratory symptoms were present in 20 out of 47 episodes (43%). In five of these 20 episodes, respiratory symptoms were the single clinical symptom at presentation. CNS symptoms were present in eight out of 47 episodes (17%). Skin lesions were present in five out of 47 episodes (11%).

The involved sites of infection are outlined in Table 4. The lungs were the most frequently affected site of infection, with pulmonary involvement observed in 44 of the 47 patients (94%). In 21 of these 44 patients, the lungs were the only site of infection. Cranial MRI was performed in 37 out of 47 patients, with CNS involvement in 16 out of 37 patients (43%). Eight out of 16 patients did not present with clinical symptoms associated with CNS infection. One of these infections was a rhino-cerebral infections, with involvement of the sinuses and without involvement of the lungs. In total, in four out of 47 patients (8.5%), the sinuses were involved. The skin was involved in five out of 47 patients (11%).

Table 3. Clinical symptoms at presentation

Symptoms at presentation	
Fever *N* (%)	29 (61.7)
Neutropenia *N*	27
Respiratory *N* (%)	20 (42.6)
Coughing *N*	11
Dyspnea *N*	6
Oxygen demand *N*	8
Other[$] *N*	7
CNS *N* (%)	8 (17.0)
Convulsions *N*	5
Reduced consciousness *N*	1
Other[#] *N*	5
Dermatological N (%)	5 (10.6)
Skin leasion(s) *N*	5
Other* *N* (%)	5 (10.6)

[$]Painful respiration; thoracic pain (stuck to breathing); thoracic pain (sharp stab), tachypnea. [#] headache; bradyphrenia; speech impediments, hand tremors, hand weakness.
*periorbital oedema, jaw pain, stomach ache, numbness in fingertips, circulatory insufficiency; acute thoracic pain.

Table 4. Localisation invasive mould disease

Localisation invasive mould disease	
Pulmonal *N* (%)	44 (93.6)
Cerebral *N*	13
Cerebral/sinuses *N*	2
Cerebral/skin *N*	1
sinuses/nasopharynx *N*	1
skin *N*	1
disseminated * *N*	4
Rhino-cerebral/skin nose/sinuses *N* (%)	1 (2.1)
Skin (disseminated) *N* (%)	2 (4.3)

*1x CNS involved.

Treatment

An overview of the IMD treatment is outlined in Table 5. For *Aspergillus* infections (including 1 mixed infection), 11 of 42 patients (26%) were treated with liposomal amphotericin B or triazole monotherapy. In 31 of 42 patients (74%) were treated with a combination therapy of liposomal amphotericin B and/or a triazole and/or an echinocandin. For *Mucorales* infections (n=3), two patients were treated with liposomal amphotericin B monotherapy and one patient with a combination therapy of liposomal amphotericin B and a triazole. For *Alternaria* infections (n=2), one patient was treated with triazole monotherapy and the other patient with amphotericin B and triazole combination therapy.

In seven out of 47 episodes (15%), local therapy was given in conjunction with systemic therapy. Local therapy of the CNS included the administration of mould-active agents using a Rickham/ Omaya reservoir (n=5) or by local treatment of the sinuses (n=2).

Table 5. Treatment IMD

IMD treatment	
Aspergillus infection N (%)*	42 (89.4)
Monotherapy with polyene or triazole *N*	11
Combination therapy with polyene and/or triazole and/or echinocandin *N*	31
Mucorales infection *N* (%)	3 (6.4)
Monotherapy with polyene *N*	2
Combination therapy with polyene and triazole *N*	1
Alternaria infection *N* (%)	2 (4.2)
Monotherapy with triazole *N*	1
Combination therapy with polyene and triazole *N*	1
Local therapy	
Rickham/Omaya reservoir *N*	5
Sinuses *N*	2
Interferon gamma *N*	1
Granulocyte transfusion *N*	1
Chirurgic procedure(s)	
Episodes *N*	17
Type of procedure(s)	
Aspergillus spp.	
Removal/drainage abscess (brain) *N*	2
Debridement (brain) *N*	2
FESS *N*	1
Lobectomy *N*	2
FESS/lobectomy *N*	1
FESS/debridement (brain) *N*	1
Debridement abscess (neck) *N*	1
FESS/adenotomy *N*	1
Mucorales spp.	
FESS/Debridement (brain) *N*	1
Lobectomy *N*	2
Alternaria spp.	
Debridement (skin) *N*	2
Aspergillus spp., Fusarium spp., Alternaria spp.	
FESS/debridement (brain/skin) *N*	1
Outcome	
Recovered without sequelae *N*	29
Recovered with sequelae *N*	9
Lobectomy *N*	4
Epilepsy, hemiparesis *N*	2
Incomplete spinal cord injury *N*	1
Convulsions *N*	1
Epilepsy, non-traumatic brain injury, visual complaints *N*	1
Died during IMD episode *N*	8
Lost to follow-up *N*	1

Abbreviations: FESS = Functional Endoscopic Sinus Surgery.
*1x mixed infection.

In 17 out of 47 patients (36%) additional surgery was performed in the context of load reduction for an *Aspergillus* infection (n=11), a *Mucorales* infections (n=3), an *Alternaria* infection (n=2) and for a mixed infection (n=1). Beyond mould-active therapy, host directed strategies, such as interferon gamma and a granulocyte transfusion, were each administered in one out of 47 episodes (2%).

Outcome

Eight of 47 patients (17%) died during the IMD episode. Seven of these deaths were likely related to IMD. One patient died because of recurrent leukaemia. In four of these seven episodes, the patient was in complete remission for ALL. Table 5 describes the outcome of the patients who developed an IMD. The 6-week mortality rate after IMD diagnosis was 10.6% (5/47), and the 12-week mortality rate was 14.9% (7/47). One patient died after 12-weeks.

Among 39 surviving patients, 29 resulted in recovery of the patients without sequelae. Nine patients recovered with sequelae, and one patient was lost to follow up.

Discussion

By evaluating a large cohort of patients treated according to the standardised treatment protocol for childhood ALL in The Netherlands, we aimed to provide insights into the epidemiology, clinical features, treatment and outcome of IMD in this vulnerable population.

The incidence rate of 7.3% for probable or proven IMD in our cohort is at the upper limit of the incidence rates ranging from 0.5% to 7.1% previously reported in paediatric (sub)populations with ALL.[4-9] In the clinical AIEOP-BFM ALL2009 trial the reported incidence of IMD was 2.6%.[6] The majority of IMD occurred during the induction and first consolidation course (week 0-10) in our cohort, which is in line with the occurrence of invasive fungal disease (IFD) described in other studies with paediatric haemato-oncology populations.[4-6, 8] The fact that these infections mainly occur during this phase of treatment can be explained by different factors, such as the use of high dose glucocorticoids, intensive chemotherapy with subsequent severe neutropenia [2, 3] and the lack of suitable prophylaxis. In 68% of our population, IMD occurred in the absence of mould-active prophylaxis. The majority of the patients with mould-active prophylaxis received itraconazole and without TDM, potentially leading to sub-therapeutic drug levels. During the early courses of ALL treatment in our study, mould-active prophylaxis

was not part of the treatment protocol during the induction course (week 0-5). This is due to the elevated risk of developing neurotoxicity when the chemotherapeutic agent vincristine is combined with azoles.[12] The high occurrence of IMD during the induction and first consolidation course emphasises the need to optimise mould-active strategies during these early ALL treatment courses. More research is needed regarding alternative regimens for mould-active strategies, such as intermittent regimens with either ambisome or echinocandins.

While the strength of this study is the uniformity of ALL treatment among our patients, its retrospective nature potentially introduces bias and difficulties compared to controlled studies. The identification of mould infections in our study was based on reported adverse events and serious adverse events, as part of the prospective ALL-11 registry.. With this approach, the 'possible' mould infections that were not reported might have been missed. Nonetheless, we believe that we were able to identify all clinically relevant, proven and probable, mould infections in our cohort. Furthermore, two researchers of our group independently categorised the reported mould-infections to reduce potential bias. The (EORTC/MSG) criteria from 2008 were used for categorisation, given the time frame of our study.

Our data shows that paediatric patients with IMD are significantly older than those who do not develop IMD. These results align with a comparable AIEOP-BFM ALL 2009 cohort, where patients aged ≥12 years had a significantly higher risk of developing IMD.[6] Existing literature indicates that treatment toxicity is typically less severe in younger children compared to older children[13], but the biological basis for this phenomenon remains unclear. Further studies should examine this phenomenon in more detail to understand whether mould-active strategies need to be stratified based on age.

The majority of our patients were routinely screened by assessing serum galactomannan during neutropenia. A positive galactomannan result was the trigger for further diagnostic work-up in only 11% of the episodes. These results indicate that the value of serum galactomannan as early marker for IMD is limited in children with ALL. These results are in contrast with the ECIL-8 guidelines, which suggests comparable performance of serum galactomannan testing between children and adults.[14] Nonetheless, the performance of the serum galactomannan test diminishes with the administration of mould-active agents. Consequently, serum galactomannan screening should be restricted in patients receiving mould-active agents.[14]

The clinical symptoms observed at initial presentation in our paediatric cohort were unspecific, with persistent fever and respiratory symptoms being the most prevalent symptoms. Among the affected sites, the significant involvement of the CNS is noteworthy. Particularly as half of these patients were initially asymptomatic. Our findings are consistent with a cohort of paediatric patients receiving chemotherapy or undergoing HSCT with proven or probable IFD with CNS involvement. Almost one-third of these patients did not initially present with neurological symptoms.[15] This finding underscores the consideration of early imaging for detecting CNS involvement, regardless of CNS symptoms. In an earlier case report comparable results were found regarding CNS involvement and the authors advise screening of extra-pulmonary sites.[16] Furthermore, these findings are in line with the ECIL-8 guidelines, where cranial imaging is recommended in patients with proven or probable pulmonary fungal infection, irrespective of CNS symptoms.[14]

Suitable prophylactic strategies need to be explored, specifically during high risk treatment courses as the induction and first consolidation course. We have started a new prophylactic strategy with twice-a-week micafungin during the induction course from August 2018. The use of prophylactic itraconazole is currently optimized by introducing TDM. Regarding IMD treatment, the voriconazole resistance frequency for *Aspergillus* isolates was 21% in our population. As this percentage exceeds the 10% resistance threshold, initial combination therapy in this population seems therefore justified.[17]

The impact of IMD in children with ALL has not extensively been described. In the recently published study with a AIEOP-BFM ALL 2009 cohort, of which the treatment protocol closely relates to the ALL-11 protocol, the 6 week mortality rate was 10.7%, and the 12-week mortality rate was and 11.2%.[6] These findings closely align with the rates observed within in our paediatric cohort.

In conclusion, the findings from our study contribute to the existing knowledge of IMD in children with ALL. This knowledge could play a role in refining diagnostic and treatment strategies aiming to improve IMD management and reduce IMD mortality. Based on our findings, the necessity of galactomannan screening could be discussed, specifically during courses with mould-active prophylaxis. Additionally, the notable frequency of CNS involvement highlights the importance of implementing standard brain imaging when IMD is suspected. Future research should focus on effective prophylaxis during at-risk treatment courses, particularly during the induction and first consolidation course.

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Author contribution statement

Design of the protocol: DB, TW, WT, and RB. Data collection: DB, CP. Interpretation of the data: DB, WT, WT and RB. Data analysis: DB, CP, TW. Writing original draft: DB, TW. Critical revision draft: CP, WT, RB. Editing draft: DB, TW. All authors provided approval of the final version.

Transparency declarations

No conflicts of interest/competing interests are applicable for this work.

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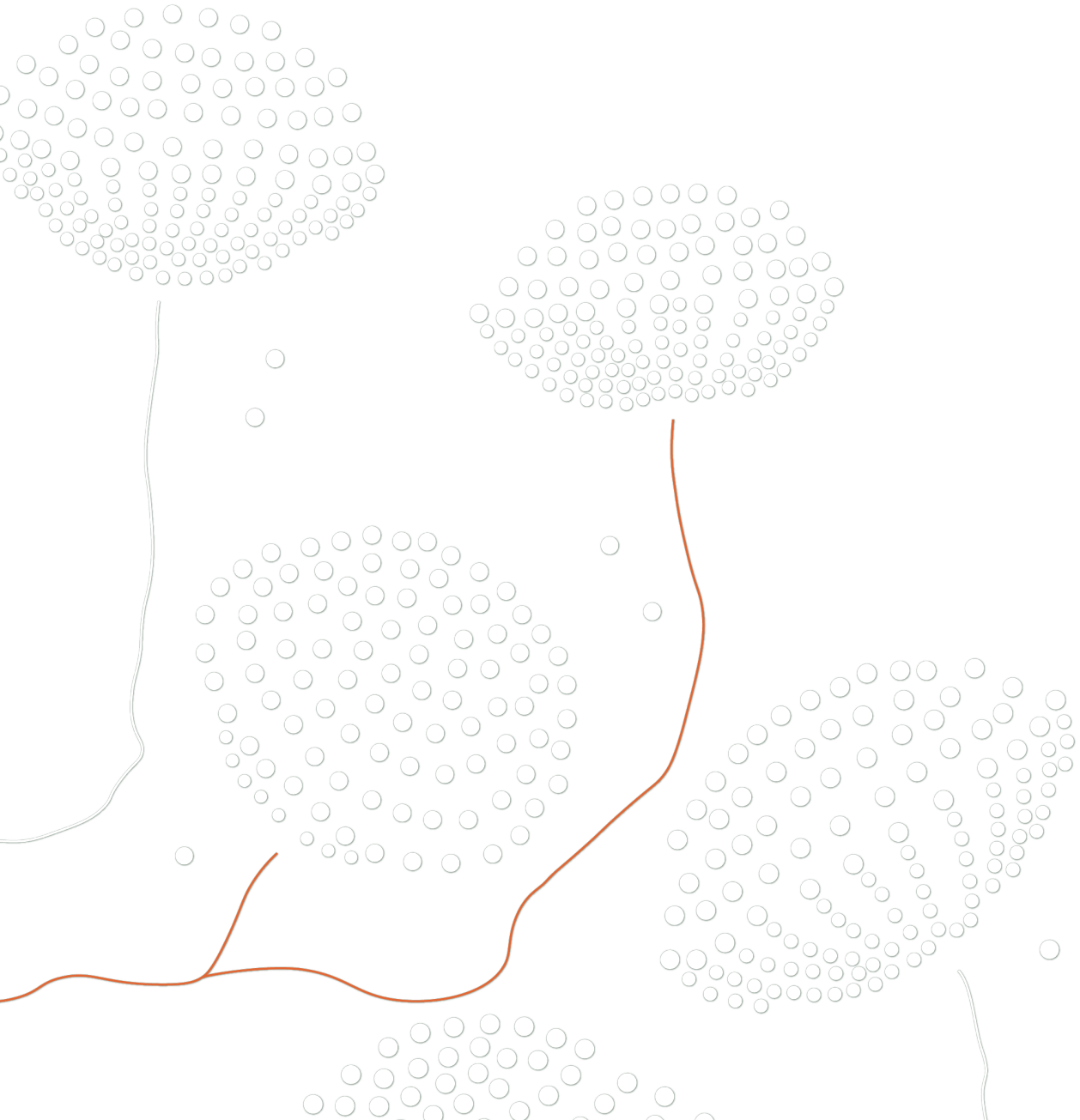
CHAPTER 3



CLINICAL PHARMACOKINETICS OF TRIAZOLES IN PAEDIATRIC PATIENTS

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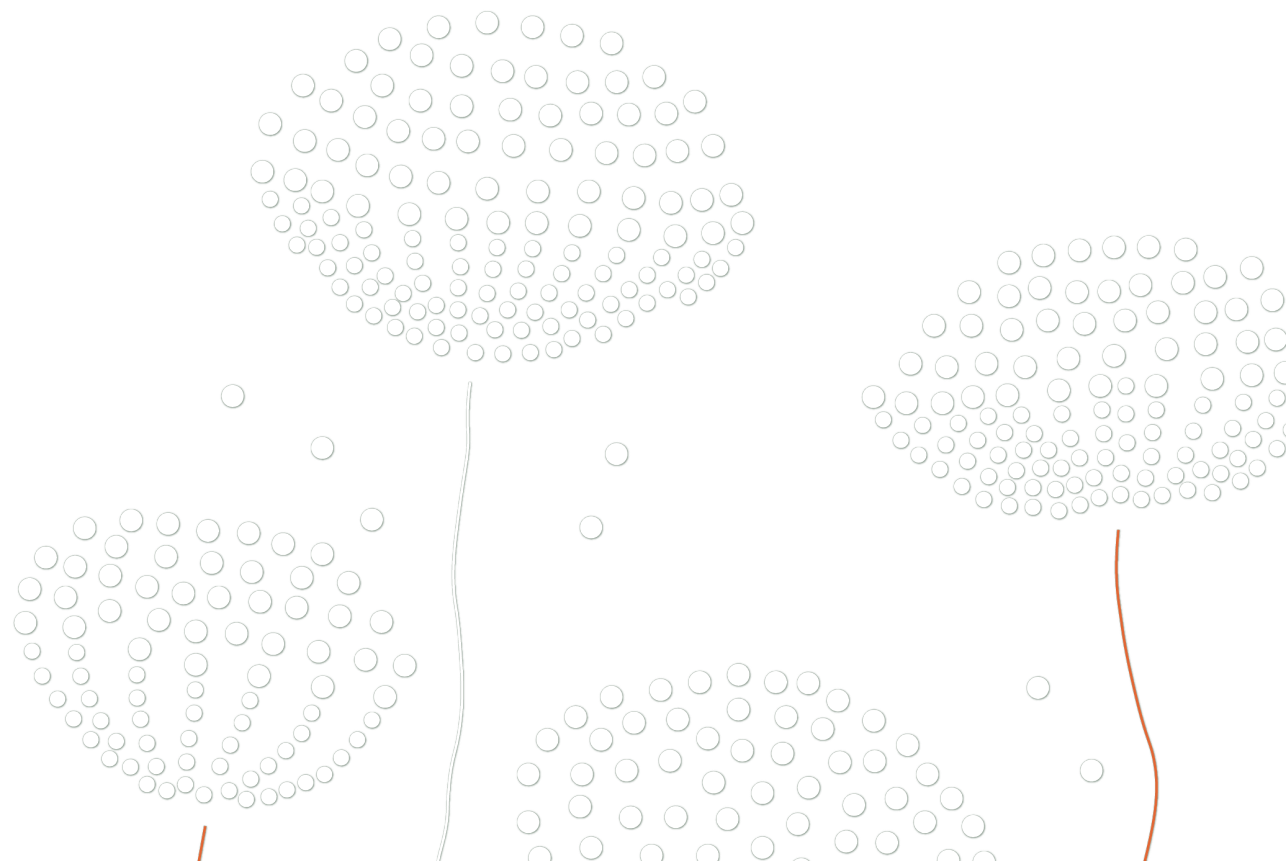

Abstract

Triazoles represent an important class of antifungal drugs in prophylaxis and treatment of invasive fungal disease in paediatric patients. Understanding the pharmacokinetics of triazoles in children is crucial to providing optimal care for this vulnerable population. While pharmacokinetics is extensively studied in adult populations, knowledge on the pharmacokinetics of triazoles in children is limited. New data are still emerging despite drugs already going off patent. This review aims to provide readers with the most current knowledge on pharmacokinetics of the triazoles: fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole. In addition, factors that have to be taken into account to select the optimal dose are summarised and knowledge gaps are identified that require further research. We hope it will provide clinicians guidance to optimally deploy these drugs in the setting of a life-threatening disease in paediatric patients.

Key points

- Fluconazole pharmacokinetics is extensively studied in the neonatal population but requires more extensive research in children and adolescents. Voriconazole pharmacokinetics is extensively studied in children and adolescents and could benefit from more information in the critically ill neonatal and paediatric population despite its limited clinical use in these populations.
- Isavuconazole, posaconazole and itraconazole pharmacokinetics are studied to a limited extend in paediatric populations. To our opinion, specifically isavuconazole and posaconazole pharmacokinetics need to be investigated, as these drugs are frequently used in the haemato-oncology setting.
- For all triazole agents there is very limited knowledge on pharmacokinetics in critically ill patients who are likely to have altered pharmacokinetics. In addition, information on the impact of dialysis, extra-corporeal membrane oxygenation as well as renal or hepatic impairment is lacking in most cases and should warrant further exploration.

Introduction

Immunocompromised paediatric patients are at high risk for invasive fungal disease (IFD). Although advances have been made in the management of IFD, incidence and mortality rates are still high whereas treatment options remain limited and challenging. Triazoles represent the most important class of antifungal drugs for prophylaxis and treatment of IFD. Within this class, isavuconazole, itraconazole, posaconazole and voriconazole are recommended for managing invasive aspergillosis[1] and fluconazole and voriconazole are recommended for managing invasive candidiasis[2, 3].

Understanding pharmacokinetics (PK) of these triazoles in paediatric patients is crucial to provide the most beneficial treatment. While the PK of triazoles is extensively studied in adult populations, knowledge on the PK of triazoles in paediatric patients is limited. Paediatric dose recommendations of triazoles have either been adjusted several times in the past years (i.e. voriconazole) or have been reported in the literature to a limited extent (i.e. isavuconazole, itraconazole and posaconazole). This review provides an overview of current knowledge on the PK of the triazoles fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole in paediatric populations and summarises factors that have to be taken into account to select the optimal dose.

Search methodology

Relevant articles that describe the PK of triazoles in paediatric patients were searched until 26-11-2020 using the databases PubMed and Embase. A detailed description of the literature search strategy is given in the supplementary file (S1). Conference abstracts and unpublished data from conference proceedings were not included in this review.

The order of appearance of each triazole in this manuscript is in the order of appearances of market introduction. This emphasises the need for more prompt action to investigate the PK for the newest released drugs and to learn from pitfalls from the past. After providing a general introduction on pharmacology for all triazoles, a general introduction of each triazole will be given including indications and dose recommendations from the current labels and guidelines. Next, triazole absorption, distribution, metabolism and elimination characteristics in adults will be described followed by relevant details on paediatric PK for both non-compartmental analyses (NCA) and population PK analyses.

Mechanism of action – pharmacology

All triazoles block the conversion of lanosterol to ergosterol through inhibition of the enzyme lanosterol 14α-demethylase (cytochrome P450 [CYP] 51). The depletion of ergosterol and accumulation of its toxic sterol precursors weaken the cell membrane structure and lead

to cell membrane dysfunction.[4-8] Next to their fungal pharmacological target, triazoles are substrates and/or inhibitors of the human equivalent CYP enzyme system.[4-8] An overview of the metabolic routes and enzyme affinities of triazoles is provided in Table 1.

Table 1. An overview of the metabolic routes and enzyme inhibition of triazoles

	Fluconazole*	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
CYP2C9	moderate inhibitor[4, 82]				substrate**/ weak inhibitor[5, 82]
CYP2C19	strong inhibitor[4, 82]				moderate substrate/ weak inhibitor[5, 82]
CYP3A4/ A5	moderate inhibitor[4, 82]	substrate**/ moderate Inhibitor[7]	substrate**/ strong inhibitor[6, 82]	strong inhibitor[8, 82]	substrate**/ strong inhibitor[5, 82]
UGT		substrate**[7]		substrate/ inhibitor**[83]	
P-gp		mild inhibitor[7]	inhibitor**[6, 82]	substrate/ inhibitor**[83]	

CYP cytochrome P450, FDA US Food and Drug Administration, P-gp P-glycoprotein, UGT uridine diphosphate glucuronosyltransferase
*Renal excretion.
**Substrate sensitivity/inhibition mentioned in FDA label and/or FDA drug interaction & labeling list, but the potency of sensitivity/inhibition is not mentioned and therefore not further specified in this table.

Fluconazole

The U.S. Food and Drug Administration (FDA) approval of fluconazole in adult patients was received in 1990 and fluconazole is licensed in individual European member states since 1988.[4, 9] Fluconazole formulations include a solution for intravenous infusion and capsules, tablets, syrup and powder for suspension for oral administration.[9] Currently, fluconazole is approved in paediatric patients aged 0-17 years for treatment of mucosal candidiasis, for invasive candidiasis and cryptococcal meningitis, for prophylaxis and treatment of *Candida* infections in immunocompromised patients, and for prophylaxis (of relapse) and treatment of cryptococcal meningitis in high risk patients.[9, 10] The fluconazole dosing recommendations in the European and American labels, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA) guidelines are given in Table 2. The recommendations in the labels are different from the international guidelines, but also differ slightly between these international guidelines. Consensus between labels and guidelines is necessary to provide good clinical practice.

Fluconazole is characterized by a bioavailability (F) of 90% in adults, which makes intravenous and different oral formulations interchangeable. Absorption of fluconazole is not affected by food intake. The volume of distribution (V_d) of fluconazole is approximately

0.7 L/kg.[4] Fluconazole shows good penetration in a variety of body fluids and tissues, like cerebrospinal fluid, sputum, saliva, urine and skin.[11] The affinity of fluconazole for plasma proteins is low (10-12%). Fluconazole is minimally metabolised (~10%) and the route of elimination is primarily (~80%) unchanged via renal excretion. Mean clearance (CL) of fluconazole is around 0.0138 L/h/kg in adults.[4]

Non-compartmental analysis of fluconazole PK in paediatric patients

Six studies described NCA of fluconazole PK in paediatric patients.[12-17] One study was performed in neonates[12] and five studies were performed in infants and children[13-17]. A detailed overview of the dosing regimens and fluconazole PK results is given in Table 3. The neonatal study included twelve premature neonates aged <24 hours after birth receiving fluconazole intravenously in a dose of 6 mg/kg with a dose interval of 72 hours.[12] The five studies in preterm and term infants and children included patients with haematological or non-haematological malignancies, congenital disease, neoplastic disease, human immunodeficiency virus (HIV), or patients with and without peritoneal dialysis (PD) after open heart surgery with an age range of 2 weeks to 16 years.[13-17] Doses of fluconazole ranged from 2-8 mg/kg per day administered either intravenously or as an oral suspension.[13-17]

Although three out of these six studies included fluconazole as an oral formulation, none of them described the relative or absolute F of fluconazole.[13, 15, 16] During the first two weeks after birth, the V_d of fluconazole in premature neonates almost doubled and CL increased more than two times.[12] After two weeks of life, the V_d of premature neonates was found to be higher compared to children.[12, 14, 15, 17] After this period, the V_d decreased[14, 15, 17] and comparable values to adults were reported in children aged ≥12 years[4, 15]. These data suggest that premature neonates aged ≥2 weeks need adequate loading doses compared to premature neonates straight after birth and that children <12 years need adequate loading doses compared to older children and adults. The higher V_d of fluconazole in premature neonates versus children and adults might be explained by characteristics of fluconazole and body composition of neonates. Fluconazole is a hydrophilic compound, and neonates tend to have a higher water: fat ratio and as such a higher V_d[18]. The increasing fluconazole CL observed in neonates during the first 2 weeks of life might be explained by the maturation of the kidney function during this period[19]. Clearance of fluconazole in premature neonates seemed to reach the same range as children 2 weeks after birth[14, 17] but was still higher compared with adults[4]. A higher maintenance dose or shorter dosing intervals might be needed in premature neonates, infants and children compared with adults. Contrary to these studies, one study in premature infants aged <3 months reported comparable CL to adults, after a single dose of fluconazole[15]. Three studies described exposure of fluconazole

after different dosing regimens and found a dose-proportional increase in exposure[15-17]. In patients with PD, no statistical differences in V_d and CL were reported compared to non-PD children with mild renal dysfunction. However, the elimination half-life of fluconazole was significantly longer in PD patients. This points towards the need for a lower maintenance dose or a longer dosing interval in this paediatric PD population.[14] To our knowledge, no other disease variables, such as HIV, have been found to alter exposure of fluconazole.[15-17]

Population pharmacokinetic analysis of fluconazole in paediatric patients

Eight population pharmacokinetic studies were conducted that included either neonatal patients[20, 21], a mixed patient population of neonates and infants[22-27] or children and adolescents aged 3 days to 15.9 years[28]. One study pooled data from three previously reported studies.[26] A detailed overview of the dosing regimens and fluconazole PK results is given in Table 4. The following patient groups were included in these studies: preterm and term patients at risk for IFD, patients with suspected or documented oral or invasive *Candida* infections, patients supported with extracorporeal membrane oxygenation (ECMO) or immunocompromised haemato-oncology patients. Eight studies described fluconazole PK in a one-compartment model[20-27], of which two studies included first-order absorption in the pharmacokinetic model.[20, 21] One study described fluconazole data best with a two-compartment model and first-order absorption.[28] The pharmacokinetic models and tested covariates are summarized in Table 5.

Overall, population pharmacokinetic studies showed that the relative F ranging from 90.9-100%[20, 21, 28] in neonates, infants and children was excellent, and was comparable to a F of >90% in adults[4]. The rate of oral bioavailability (K_a) ranged from 0.538-3.76 h^{-1}.[20, 21, 28] It is difficult to compare values of V_d and CL between fluconazole population pharmacokinetic studies directly, as a variety of covariates were included on V_d and CL. Allometrically scaled bodyweight with fixed[20, 21, 23] and/or estimated[20] exponents was added on either V_d[20, 21, 23] and/or CL[20, 21, 23]. Age (inversely related)[27], ECMO[25] or a coefficient for ECMO[26] and/or linearly scaled bodyweight[26, 28] were included as covariates on V_d. Covariates as linearly scaled bodyweight[26], body surface area[28] and exponents for estimated glomerular filtration (estimated)[20], serum creatinine[21, 23-26], postmenstrual age (PMA) as a function of gestational age (GA) and postnatal age (PNA)[21], gestational age at birth (BGA)[23] and/or PNA[23], were included on CL. Serum creatinine was inversely related to CL.[21, 23-26] In one study it was not clear if postmenstrual age was included as covariate on fluconazole CL in the final model.[22] Another study reported that bodyweight influenced fluconazole CL but did not report the covariate equation.[22] Three studies used linear regression analysis to test covariates.[24, 25, 28] One study concluded that fluconazole CL in premature neonates was low at birth and

doubled within the first month after birth, but did not report on changes in fluconazole V_d.[23] This conclusion is slightly different from a previous NCA report, which reported a more than two fold increase in CL during the first 2 weeks of life. Another study included both ECMO and non-ECMO patients and reported a significantly higher V_d but similar CL in paediatric ECMO patients compared to non-ECMO patients.[26] This higher V_d is likely due to the hydrophilic nature of fluconazole and the large circulating volume of ECMO procedures[29]. These population pharmacokinetic results point toward the need of an adequate loading dose of fluconazole in paediatric ECMO patients.

Physiologically-based PK of fluconazole

Two studies have obtained interesting pharmacokinetic information with physiologically-based pharmacokinetic (PBPK) models and assessed fluconazole dosing by predicting either cerebrospinal fluid exposure or the influence of ECMO.[30, 31] Data from plasma samples of 166 infants (<750 grams) with a median PNA of 21 days (range 3-93 days) and cerebrospinal fluid samples of twenty-two infants with a median PNA of 28 days (range 24-33 days) showed fluconazole exposure in the central nervous system, with a central nervous system-to-plasma ratio of ~1.[30] In the second study, the oedema disease state of ECMO patients was added to the model and the authors suggested that oedema contributes to lower fluconazole exposure.[31]

Summary of findings and recommendations

- Pharmacokinetic data of fluconazole in neonates and infants are abundant, and PK data of fluconazole in children and adolescents are scarce. Research topics should include the *F* of all different oral fluconazole formulations and full pharmacokinetic investigations in children and adolescents. Special patient populations such as critically ill paediatric patients with renal impairment or other renal replacement therapy and solid organ transplant recipients should be further investigated. Additionally, the influence of the disease state of patients, such as excess fluid retention, on fluconazole PK might be interesting to further explore.
- The relative *F* of fluconazole in paediatric patients is comparable to the *F* described in adults, which suggests that different formulations of fluconazole are interchangeable in paediatric patients. Most of these studies included the suspension as oral formulation, data on *F* of other oral formulations are very limited in paediatric patients.
- Non-compartmental analyses report a higher V_d in preterm neonates compared to children and adults. These results suggest that adequate loading doses are needed. In preterm neonates the fluconazole CL increases during the first 2 weeks after birth. The

CL after 2 weeks of birth is comparable to the CL in children but higher as compared to the CL in adults. These results imply that higher maintenance doses or shorter dosing intervals are needed in preterm neonates and children. Non-compartmental analysis in paediatric PD patients report a significantly increased elimination half-life for fluconazole and these data suggest a lower maintenance dose or a longer dosing interval in this paediatric population.

- Population PK studies report that allometrically scaled bodyweight and ECMO are significant covariates on $V_{d.}$. As a consequence, paediatric patients receiving ECMO might need higher loading doses. Allometrically scaled bodyweight, serum creatinine (inversely related) and either PMA (as a function of GA and PNA), or GA and PNA are significant covariates on CL. Dose adjustments based on serum creatinine, GA and PNA might be taken into account to optimize fluconazole use. A standardised method to report both allometric scaling and maturation would be useful to compare pharmacokinetic results from different studies and populations.
- Dose recommendations for fluconazole are inconsistent between the labels and the ESCMID and IDSA guidelines. As outlined previously by others[22], agreement between labels and international guidelines is necessary for clinical practice. Currently, there is no possibility to translate expert consensus from guidelines to an updated product information sheet. A reference in the summary of product characteristics to relevant guidelines would be an option to cover this. However, the legal background to make it possible for authorities and the pharmaceutical industry to request and update their product information will be tremendously challenging.

Itraconazole

Itraconazole was approved for adult patients in 1992 by the FDA[6] and itraconazole has been licensed in individual European member states. The oral capsules and oral solution are widely available in contrast to the intravenous formulations.[32] Itraconazole is not approved in paediatric patients <18 years.[6, 33] However, the paediatric ESCMID-ECMM guideline for invasive aspergillosis and the paediatric ESCMID guideline for invasive candidiasis recommend a dose of 2.5 mg/kg twice daily of the oral solution for the purpose of mould- and yeast-active prophylaxis in children aged 2-18 years.[1, 2] For treatment of a proven or probable invasive aspergillosis, itraconazole is recommended in a loading dose of 5 mg/kg twice daily of the oral solution on day 1, followed by 2.5 mg/kg twice daily in patients aged 2-18 years.[1]

In adults, itraconazole has a variable F with an absolute oral F of the oral solution of 55%[6]. The F of the oral solution is ~30% higher compared to the oral capsules[34]. Because of

the variable F between formulations, these are not interchangeable. Food intake and pH fluctuation influence the itraconazole uptake, therefore the oral capsules are advised to be administered in a fed state and the oral solution in a fasted state[35]. The V_d of itraconazole is >700 L.[6] Itraconazole penetrates into a variety of body tissues, including lung, kidney, liver, bone, stomach, spleen, muscle, keratinous tissue and skin but does not penetrate well into the cerebrospinal fluid.[36-38] Itraconazole has an active metabolite hydroxy-itraconazole with comparable in vitro activity to the parent compound. Both itraconazole (99.8%) and hydroxy-itraconazole (99.6%) are highly bound to plasma proteins. Itraconazole is mainly metabolized via CYP3A4 (Table 1). Renal elimination of both itraconazole and hydroxy-itraconazole is <1%. The inactive metabolites of itraconazole are excreted in urine (35%) and feces (54%). Mean CL of itraconazole in adults is 16.68 L/h.[6]

Non-compartmental analysis of itraconazole PK in paediatric patients

To our knowledge, there are no NCA reports of itraconazole PK described in neonates. Six studies performed a NCA of itraconazole in infants, children and adolescents aged 0.5 to 17 years at risk for mucosal fungal infection or IFD. A detailed overview of the dosing regimens and itraconazole pharmacokinetic results is given in Table 6. Patients with haematological and non-haematological malignancies, liver transplantation, respiratory tract infections, HIV, cystic fibrosis (CF), other infections/diseases or undergoing haematopoietic stem cell transplantation (HSCT) were included in these studies. Itraconazole was administered in different oral and intravenous dosing regimens for prophylaxis and/or treatment. Dosages of itraconazole ranged from 2.5-5 mg/kg once or twice daily, with or without a loading dose of 5 mg/kg twice daily.[39-44]

In five studies itraconazole was administered as an oral solution[40-44], of which one study also included the intravenous formulation but the authors did not report the F of itraconazole[40]. Three studies stratified pharmacokinetic results of itraconazole by age[39, 42, 43]. A single dose of 2.5 mg/kg or multiple dosing regimens of 5 mg/kg once daily or 2.5 mg/kg twice daily have been investigated in patients aged 0.5-2 years, 2-5 years and/or >5 years.[39, 42, 43] Exposures differ widely between groups and studies. Both CL and V_d appear to change strongly within these groups. Interestingly, administration of a 2.5 mg/kg twice daily regimen resulted in much higher itraconazole and hydroxy-itraconazole exposures compared with a 5 mg/kg once daily regimen of itraconazole[42-44]. This is possibly owing to saturable absorption. One study in patients undergoing HSCT reported a considerably higher exposure compared with other studies, which is most likely explained by including a loading dose for itraconazole (5 mg/kg twice daily on day 1, followed by 5 mg/kg once daily) and pharmacokinetic sampling after the third administered dose[40]. Special paediatric populations, such as patients with

HIV, showed comparable exposures of itraconazole and hydroxy-itraconazole to other populations, while patients with CF showed a considerably lower exposure after 2.5 mg/kg itraconazole twice daily compared with other paediatric populations[41, 44]. Higher dosages than 2.5 mg/kg twice daily might be needed in paediatric patients with CF.

Population pharmacokinetic analysis of itraconazole in paediatric patients

Two population pharmacokinetic studies in paediatric patients have been published[39, 45]. A detailed description of the dosing regimens and itraconazole pharmacokinetic results is given in Table 7. The pharmacokinetic models and covariates tested are summarised in Table 8.

In 33 patients at risk for IFD aged 0.5 to 17 years, itraconazole was given intravenously as a single 2.5 mg/kg dose. Underlying diseases included CF, malignancies with febrile neutropenia, respiratory tract infections or other diseases/infections. A three-compartment model best fitted the data for itraconazole. All parameter estimates were scaled to a total body weight of 30 kg[39], but the covariate equations were not reported.

In 49 patients with CF and undergoing bone marrow transplantation aged 0.4 to 30 years, including five adult patients, a median itraconazole dose of 5.4 mg/kg was given orally as capsules or solution. The vast majority of patients received itraconazole in a once daily regimen. A one-compartment model was used with delayed absorption and included both itraconazole and hydroxy-itraconazole. The K_a for the solution and capsules was 0.96 h^{-1} and 0.09 h^{-1}, respectively. The relative F of capsules was 0.55 compared to the solution. CL and V_d of itraconazole were allometrically scaled to a total body weight of 70 kg.[45] Values of exponents used for allometric scaling were not reported.

Summary of findings and recommendations

- Pharmacokinetic studies of itraconazole are limited in paediatric patients populations and are lacking in neonates. Future research should focus on retrieving pharmacokinetic data in these patient populations and should address the F of the different itraconazole formulations.
- The itraconazole oral solution is the preferred formulation, as the relative F was 45% higher compared to itraconazole capsules. Given the unknown absolute F and the difference in F of the oral formulations, dosing of itraconazole and switching between formulations should be accompanied by therapeutic drug monitoring. Furthermore, a twice daily itraconazole regimen instead of a once daily regimen is suggested to optimise itraconazole exposure.

- Non-compartmental analyses suggest a great extent of variability across different age groups, attributable to both CL and V_d. Differences in studies preclude final conclusions and does warrant further investigation. Paediatric patients with CF might need a higher itraconazole dose as a considerably lower exposure is reported compared with patients without CF.
- Population pharmacokinetic studies included allometrically scaled bodyweight on itraconazole pharmacokinetic parameters. As itraconazole and hydroxy-itraconazole are highly bound to plasma protein, the unbound drug concentrations of itraconazole and hydroxy-itraconazole could be interesting variables for future research specifically in the critically ill population. Research in critically ill populations might be of interest in resource-poor countries where posaconazole and voriconazole may not be available.
- Itraconazole is not approved for patients <18 years in the labels, but international guidelines provide a dose recommendation for patients aged ≥2 years for both prophylaxis and treatment. Agreement between labels and guidelines is important for clinical practice and needs to be established.

Voriconazole

Voriconazole was both European Medicines Agency (EMA) and FDA approved in 2002 for adult patients and has been available as oral tablets, oral suspension and powder for concentrate for solution.[5, 46] The current approved indications for both adult and paediatric patients aged ≥ 2 years are treatment of invasive aspergillosis, candidaemia in patients without neutropenia, oesophageal candidiasis, infections caused by *Scedosporium* and *Fusarium* species[5, 46], fluconazole-resistant invasive *Candida* infections and prophylaxis of IFD in high risk allogenic HSCT.[46] The labels, the paediatric ESCMID-ECMM guideline for invasive aspergillosis and the paediatric ESCMID invasive candidiasis guideline give dose recommendations for paediatric patients aged ≥2 years. For prophylaxis and treatment of both invasive aspergillosis and candidiasis, a loading dose of 9 mg/kg two times daily on day 1, followed by 8 mg/kg twice daily intravenously or 9 mg/kg (max. 350 mg) twice daily for the oral formulations in paediatric patients aged 2-11 years or aged 12-14 years (<50 kg) is recommended. A loading dose of 6 mg/kg twice daily on day 1, followed by 4 mg/kg twice daily intravenously or 200 mg twice daily for the oral formulations is recommended in paediatric patients aged 12–14 years (≥ 50 kg) or aged ≥14-15 years.[1, 2, 5, 46]

In adults, voriconazole is characterized by a F of 96% for both tablets and suspension[5], which makes it possible to switch between the two available formulations. As food intake can reduce voriconazole absorption, both oral formulations are advised to be administered in a fasted state[5, 47]. The V_d of voriconazole is around 4.6 L/kg.[5] The distribution of voriconazole

is suggested to be extensive into different body tissues, including the cerebrospinal fluid [48] and aqueous and vitreous parts of the eye[49]. Voriconazole is bound to plasma proteins for around 58%[5]. Voriconazole is characterized by nonlinear pharmacokinetics in adult patients. The main CYP450 enzyme involved in the metabolism of voriconazole is CYP2C19 with also CYP2C9 and CYP3A4 playing a less prominent role (Table 1). Elimination via renal excretion accounts for only 2% in its unchanged form.[5, 46]

Non-compartmental analysis of voriconazole PK in paediatric patients

There are no NCA of voriconazole PK available in neonates and infants. Five NCA are available in paediatric patients aged 2 to 17 years. A detailed overview of the dosing regimens and voriconazole pharmacokinetic results is given in Table 9. Patients with haematological and non-haematological malignancies and patients undergoing BMT or HSCT were included in these studies. Voriconazole was administered either orally or in a combined intravenous to oral regimen. The oral voriconazole dose was from 4 to 9 mg/kg (max. 350 mg) twice daily or was fixed at 200 or 300 mg twice daily. The intravenous voriconazole dose was from 4 to 8 mg/kg twice daily, either with or without a loading dose of from 6 to 9 mg/kg twice daily.[50-54]

Overall, only one study reported the F of voriconazole ranging from 43.6-90.0%.[52] This F in paediatric patients was lower compared with the F of 96% seen in adults.[5] In the other studies a lower F was hypothesized, as lower exposures were reported after oral administration compared to exposures after intravenous administration[50, 51, 54]. Unlike observations in adults where food intake reduces voriconazole absorption[5, 46], it remains unclear if the influence of food intake attributes to the variable F of voriconazole in paediatric patients. The reported lower F and subsequent lower exposure after oral administration imply that there is no bioequivalence between intravenous and oral formulations of voriconazole in paediatric patients. Two studies stratified pharmacokinetic results of voriconazole by age[52, 54]. One of these studies reported an overall comparable exposure of voriconazole in the group aged 2-5 years and aged 6-11 years after administration of 4, 6 or 8 mg/kg voriconazole in a twice daily intravenous to oral regimen. This study also reported a ~2.5 times increased exposure after increasing voriconazole from 4 to 8 mg/kg, suggesting non-linear PK in these paediatric patients over a dose range of 4-8 mg/kg.[52] The other study administered voriconazole according to the current labels and guidelines. For a detailed description of the dosing strategies see Table 9. This study reported that patients aged 12-14 years (<50kg) had a higher exposure compared to patients aged 2-11 years and that patients aged 12-14 years (≥50 kg) had a lower exposure compared to patients <15 years (<50 kg).[54] The sample sizes in the different age

groups were small and the authors mentioned that the CYP2C19 genotype in their Asian population might have played a role in the differences in voriconazole PK.[54] Two studies showed an overall higher exposure of voriconazole compared to the other studies.[53, 54] This higher exposure might be explained by the higher dosing regimens used.

Population pharmacokinetic analysis of voriconazole in paediatric patients

There are no population pharmacokinetic analyses of voriconazole available in neonates. One study included infants, but did not describe the PK results for this population separately.[55] In total, nine studies were performed in paediatric patients aged 0.8 to 21 years[55-63], of which two studies pooled data of three earlier published studies[57, 62] and included data of healthy adult patients[57]. A detailed overview of the dosing regimens and voriconazole pharmacokinetic results is given in Table 10. These studies included immunocompromised patients with haematological or non-haematological diseases, immunodeficiency or autoimmune diseases, liver transplantation, CF, other infections/ diseases or undergoing HSCT or BMT.[55-63] Voriconazole was administered either intravenously[55, 61, 63], orally[55] or in a combined intravenous to oral regimen[56-60, 62]. All studies reported PK of voriconazole in a two-compartment model[55-62] and one study included also one compartment for the metabolite of voriconazole[63]. The models included delayed absorption[55, 57, 59] and first order absorption [55-60, 62] and either linear[61], nonlinear [55, 56, 58, 60, 62] or mixed linear and nonlinear elimination[57, 59]. In one study, voriconazole elimination was included as linear CL but in addition also as non-linear CL to its metabolite[63]. Two other studies included both concentration-dependent and time-dependent voriconazole elimination.[57, 59] The PK models and covariates tested are summarized in Table 11.

Seven studies in paediatric patients administered either an oral solution or tablets of voriconazole in which F was from 44.6%-85%.[55-60, 62] The F found in these studies was also lower compared to the F of 96% reported in adults.[5] Similar to findings in the NCA, it remains unclear if the influence of food attributed to this difference. The K_a ranged from 0.43-1.53 h^{-1}[55-60, 62]. Allometrically scaled bodyweight with fixed exponents[56-60, 63] was added on either clearance(s)[57, 59, 63], V_d [57-60, 63] and/or maximum rate of enzyme activity (V_{max})[56-60, 63]. Two studies included patients aged <2 years[55, 63], of which one study had sufficient information to include a maturation factor to the pharmacokinetic model[63]. Two other studies incorporated CYP2C19 genotype[61, 62],alanine aminotransferase (ALT)[61, 62], and alkaline phosphatase (ALP) on CL. In these studies CYP2C19 genotype in the combined group of heterozygous extensive/poor CYP2C19 metabolizers[61, 62], ALT[61, 62] and ALP[61] significantly decreased CL, but according to the authors these variables were not predictive for voriconazole CL[61, 62]. Other covariates included linearly scaled weight and age on CL and V_d[55].

Physiologically-based PK of voriconazole

One PBPK model was developed for voriconazole in children. The PBPK-derived values from the initial oral model showed an overprediction for F, area under the curve (AUC), and maximum serum concentration (C_{max}) in children, which decreased substantially after adding intestinal CL to the model. Intestinal first pass metabolism might explain the lower bioavailability of voriconazole in children compared with adults.[64]

Summary of findings and recommendations

- The PK of voriconazole in neonates and infants and children aged <2 years is lacking, and future studies should take these patient populations into account. Future research should further focus on the highly variable F, differences in F between the oral formulations, the linear or non-linear relationship of voriconazole elimination and PK in critically ill paediatric patients.
- None of the reports highlight the difference in F of the oral solution and tablets. In contrast to adults, it seems that there is no bioequivalency between oral and intravenous formulations in paediatric patients. It is unclear if the intake of food or gastric-emptying time is (partly) responsible for this variability and/or if the influence of intestinal first pass metabolism might play a role. These questions need to be further explored. Switching from intravenous voriconazole to oral formulations cannot be done as straightforwardly as in adults but should be accompanied by therapeutic drug monitoring.
- Non-compartmental analyses report that patients aged <12 year seem to have a higher CL and V_d compared to patients aged ≥12 years and therefore the recommended loading dose and maintenance doses of voriconazole is higher in patients aged 2-11 years compared with those above 12 years.
- Some population pharmacokinetic studies reported that the CYP2C19 genotype and ALT values were significant covariates on voriconazole CL, but were not predictive for voriconazole CL. Although CYPC19 might be correlated with voriconazole CL, upfront dose adjustments in clinical practice are not yet advised in populations with a low prevalence of homozygous allele variations. Further research is needed to explain the differences of voriconazole PK in paediatric patients, to explore the influence of CYP2C19 and to reflect on the role of ALT as a surrogate marker for liver function. Additionally, other possible elimination routes (i.e. flavin-containing monooxygenase 3[65]) might be interesting topics to explore.

Posaconazole

In 2005, posaconazole received EMA marketing authorization and in 2006 FDA approval for adult patients.[8, 66] The currently available formulations include a concentrate for solution for infusion, an oral suspension and gastro-resistant tablets.[66] The FDA approved posaconazole in paediatric patients aged >13 years for prophylaxis and treatment of invasive aspergillosis and invasive candidiasis[8], but in Europe posaconazole is not approved in paediatric patients <18 years[66]. Both the new solid oral tablet and the intravenous solution of posaconazole require a loading dose of double the maintenance dose, whereas this loading dose is not of value for the marketed oral suspension. In the paediatric ESCMID-ECMM guideline for invasive aspergillosis, the recommended dose for posaconazole prophylaxis for patients aged ≥13 years is 300 mg once daily of the gastro-resistant tablet or a dose of 200 mg three times daily of the marketed oral suspension. For salvage therapy of a proven/probable invasive aspergillosis for patients aged ≥13 years, 300 mg once daily of the gastro-resistant tablet or intravenous formulation or a dose of either 400 mg twice daily or 200 mg four times daily of the marketed oral suspension is recommended.[1] The posaconazole dosing in the setting of prophylaxis for invasive candidiasis is identical to the dosing regimen of the marketed oral suspension for prophylaxis of invasive aspergillosis.[2]. All the above mentioned guidelines recommend to use the gastro-resistant tablet over the marketed oral solution because of the anticipated more favorable oral bioavailability of the gastro-resistant tablet.

The F of posaconazole is only reported for adult patients receiving the gastro-resistant tablets and is around 54%.[8] As the F of the marketed oral suspension is not available in the public domain, bioequivalence between the formulations cannot be assured. Both the marketed oral suspension and gastro-resistent tablets show saturable absorption, but for the gastro-resistant tablets this was only seen for daily doses above 800 mg posaconazole.[67, 68] Absorption of the marketed posaconazole suspension is significantly influenced by food intake and administration in fed state is advised.[69] The gastro-resistant tablets are less prone to food effects[66], but a fed state can still increase the absorption by ~1.5 times[70]. The tablet cannot be broken due to the gastro-resistant coating, which makes it difficult to administer these tablets to patients who are unable to swallow. The mean apparent V_d (V_d/F) of posaconazole is 287 L for the gastro-resistant tablet and the V_d/F is around 1774 L for the marketed oral suspension.[8] Posaconazole penetrates into a variety of tissues, including the lung, heart, kidney, liver, but penetrates poorly into brain tissue[71] and cerebrospinal fluid[72]. Posaconazole is bound to plasma proteins for >98%.[8] In contrast to the other azoles, posaconazole is metabolized via uridine diphosphate

glucuronosyltransferase (UGT) enzymes, and particularly UGT1A4 (Table 1)[73]. About 77% of radioactive labeled posaconazole was retrieved in the feces of which 66% was the parent compound. The formed metabolites that were excreted in urine and feces accounted for about 17% of the radioactive labeled posaconazole.[8, 66] Mean CL is 7.3 L/h.[8]

Non-compartmental analysis of posaconazole PK in paediatric patients

Currently, there are no NCA of posaconazole PK performed in neonates. A detailed overview of the dosing regimens and posaconazole PK results is given in Table 12. Three NCA were performed in immunocompromised patients aged 3 months to <18 years.[74-76] Patients with haematological and non-haematological malignancies or undergoing HSCT were included in these studies. In two studies, posaconazole was only administered as the marketed oral suspension. The relative F of posaconazole was not determined in these studies[74, 75]. In the other study, posaconazole was administered as a not yet marketed new formulation, a powder for oral suspension (PFS), as well as an intravenous solution[76]. The first NCA investigated posaconazole orally as the marketed suspension at 6 or 9 mg/kg in a two or three times daily regimen in three different age groups[74]. The second study used the marketed oral posaconazole suspension as 120 mg/m^2 based on body surface area (BSA)[75]. In the third study, posaconazole was investigated as either intravenous solution or as the new oral PFS at 3.5 mg/kg, 4.5 mg/kg or 6 mg/kg in a twice daily regimen on day 1, followed by the same dose in a once daily regimen in two different age groups[76].

Increasing the daily dose from 6 mg/kg to 9 mg/kg or increasing the dosing frequency of the marketed suspension from two times daily to three times daily did not increase exposure of posaconazole. This suggests saturable absorption in paediatric patients, which is also seen in adults. The authors suggested that children aged >7 years showed higher exposures compared to patients aged 2-7 years[74], implying that higher dosages are needed in younger patients to achieve a comparable exposure to older patients. A dosing regimen based on BSA resulted in a comparable mean exposure as children aged 7-17 years on a 6 mg/kg twice daily regimen.[75] However, data based on BSA was not available for different age groups and exposure in the youngest patients is therefore not exactly known with this approach. Administering posaconazole intravenously or as a PFS in a once daily regimen (with a loading dose on day 1) resulted in higher exposures compared to the exposures after a twice daily regimen of the marketed oral suspension in the previously described report[74, 76]. Similarly to this earlier report, posaconazole exposure was lower in younger patients compared to older patients in all dosing groups[74, 76]. Furthermore, the exposure after oral PFS administration was lower compared to intravenously administered posaconazole. As suggested by the authors there seems to be no bioequivalence between the intravenous and new PFS formulations in paediatric patients.[76]

Population pharmacokinetic analysis of posaconazole in paediatric patients

Currently, there are no population pharmacokinetic studies of posaconazole performed in neonates. One population pharmacokinetic model was published in 117 immunocompromised infants, children and adolescents aged 0.5 to 18 years. A detailed overview of the dosing regimens and posaconazole pharmacokinetic results is shown in Table 13. Posaconazole was administered as the marketed suspension in the vast majority of these patients, with a mean daily dose of 13.11 mg/kg.[77] A one-compartment model fitted the data best. An overview of the pharmacokinetic model and covariates tested is given in Table 10. Allometrically scaled bodyweight was added on CL and V_d and covariates such as diarrhea and concomitant use of proton pump inhibitors decreased posaconazole bioavailability only after administration of the marketed suspension.[77] The pharmacokinetic models and covariates tested are summarized in Table 14.

The relative K_a of the marketed suspension and tablets was 0.197 h^{-1} and 0.588 h^{-1}, respectively. The relative F of the marketed suspension and tablets was not described. A decrease of 33% in relative F of the marketed suspension was seen in patients with diarrhea and a 42% decrease in patients using proton pump inhibitors (PPI). As only the oral marketed formulations were used, V_d/F and apparent CL (CL/F) were determined. Allometrically scaled bodyweight normalised to 70 kg was added as covariate on posaconazole V_d/F and apparent CL.[77]

Summary of findings and recommendations

- Paediatric pharmacokinetic data of posaconazole is very limited, and future research is particularly needed to explain PK of posaconazole in infants, and to further resolve its PK in children and adolescents. Research topics should include the F of all the oral formulations and the PK in critically ill patients and patients with CF. Furthermore, the drug-drug interaction between posaconazole and CF transmembrane conductance regulator modulators might be an interesting research topic. In adults, the gastro-resistent tablets are the preferred formulation, but there are no pharmacokinetic data of this formulation available in paediatric patients. This oral tablet formulation urgently needs to be studied in children and adolescents to confirm that this is the most appropriate oral pharmaceutical formulation to be used. For patients who are unable to swallow tablets, the new PFS needs to be further explored. Other new child-friendly formulations allowing administration of smaller dosages might be needed to further expand posaconazole treatment.
- Although all studies administered posaconazole as an oral formulation, the absolute and/or relative F were not described and need to be explored in paediatric

patients. Exposures after administration of the not yet marketed posaconazole PFS were lower compared to intravenous administration, and suggests that there is no bioequivalence between these two formulations. Given the unknown F of the marketed formulations and the non-bioequivalence between intravenous and PFS formulations, dosing of posaconazole and switching between formulations should be accompanied by therapeutic drug monitoring.

- The majority of available paediatric NCA only administered the suspension of posaconazole as oral formulation. These data confirm adult observations that the marketed suspension shows saturable absorption. The new posaconazole PFS, that is not yet on the market, shows higher exposures in a once daily regimen compared to the twice daily regimen of the current marketed posaconazole suspension. After administration of both oral and intravenous formulations, posaconazole exposure seems lower in younger patients and higher dosages might be needed to reach the same exposure as older patients.
- The population pharmacokinetic study included allometrically scaled bodyweight on CL and V_d. Diarrhea and concomitant use of proton pump inhibitors were negatively associated with the relative F of the marketed posaconazole solution. Because of the high protein binding of posaconazole, it might be interesting to explore the influence of unbound drug concentrations on posaconazole PK.

Isavuconazole

The relatively new triazole isavuconazole is not licensed for paediatric patients. The EMA approved isavuconazole for adult patients in 2014 and the FDA approved isavuconazole in 2016.[7, 78] Available formulations include an oral formulation as hard capsules and an intravenous formulation as powder for concentrate for solution. In adult patients isavuconazole is indicated for the treatment of invasive aspergillosis. In addition, it is licensed for mucormycosis for patients who have a contraindication or intolerance for amphotericin B.[7, 78] Isavuconazole has not yet been approved for paediatric patients and the international guideline does not provide recommendations for dosing of isavuconazole in paediatric patients.[1] Dose finding trials have been completed or are ongoing, so more information is expected soon.

Isavuconazole is given as a pro-drug isavuconazonium sulfate. The oral F of isavuconazonium sulfate is 98% in adults.[7] After a rapid and complete absorption, isavuconazonium sulfate is quickly and completely cleaved to isavuconazole.[7] Oral and intravenous formulations can be used interchangeably. Food intake or fluctuations in pH do not influence the absorption of isavuconazole[79]. Based mostly on animal research,

isavuconazole widely distributes in different tissues, including liver, lungs, eyes, kidneys, skin, bone, nasal mucosa and brain.[80] Isavuconazole is bound to plasma proteins for >99% and is metabolized by CYP3A4/A5 and UGT (Table 1).[7]

To our current knowledge, there is only one paediatric study of isavuconazole available in the public domain outside of conference abstracts and case reports. This retrospective study included 29 patients with a haematological malignancy aged 3-18 years. In six patients, an 8-point sample curve was obtained over 12 hours. The demographics and dosing regimens are not reported for these six patients separately. The median $AUC_{0\text{-}12h}$ (range) in these six patients was 153.16 mg × h/L (86.31-169.45).[81] Because of the small sample size and missing demographics and dosing information it is difficult to draw any conclusions from these data.

Summary of findings and recommendations

Data on the PK of isavuconazole are urgently needed in paediatric patients including population paediatric pharmacokinetic data. Specifically for paediatric patients, information on F including information on dosing via a nasogastric tube are needed, as well as information on bioequivalence after intake of whole or opened capsules. As isavuconazole is highly protein bound, more research is needed on unbound drug concentrations in for instance the critically ill patient populations.

Conclusions

This review shows that the PK of fluconazole are extensively studied in the neonatal population and the PK of voriconazole are extensively studied in children and adolescents. Isavuconazole, itraconazole and posaconazole are studied to a limited extend. Fluconazole data in children and adolescents are understated, while for other triazoles pharmacokinetic data in neonates and infants urgently need to be studied. Future studies should explore PK of the newest triazole agents, understanding the F of the available formulations and learning more about interactions with food or administration over a nasogastric tube, the effect of CYP genotypes and other metabolic routes, the influence of other factors such as unbound drug concentrations for highly protein bound agents and the development and PK of new oral formulations that can easily be deployed in paediatric patients. In addition, information on the PK of triazoles in critically ill patient populations, the impact of dialysis, ECMO as well as renal or hepatic impairment is lacking in most cases and should warrant further exploration. Better understanding of the PK is necessary for optimal clinical care and remaining knowledge gaps will need to be clarified.

Table 2. Fluconazole dose recommendation in European and American labels and international guidelines.

		Europe*[10]	
		Prophylaxis	**Treatment**
Neonates	Preterm neonates (PNA 0-14 days)		
	Preterm neonates (PNA >14 days)		
	Term neonates (PNA 0-14 days)	3-12 mg/kg (max. 12 mg/kg) every 72 hours#	(Loading dose 6 mg/kg, on day 1)# 3-12 mg/kg (max. 12 mg/kg) every 72 hours#
	Term neonates (PNA 15-27 days)	3-12 mg/kg (max. 12 mg/kg) every 48 hours#	(Loading dose 6 mg/kg, on day 1)# 3-12 mg/kg (max. 12 mg/kg) every 48 hours#
	Neonates (<1000g)		
	Neonates (No PNA or GA reported)		
Infants/children/adolescents	Age: 28 days to 11 years	3-12 mg/kg (max. 400 mg/day) every 24 hours#	(Loading dose 6 mg/kg, max 400 mg, on day 1)# 3-12 mg/kg (max. 400 mg) every 24 hours#
	Age: 12 to 18 years	3-12 mg/kg (max. 400 mg) every 24 hours#	(Loading dose 6-12 mg/kg, max 800 mg, on day 1)# 3-12 mg/kg (max. 800 mg) every 24 hours#
	Infants (No age range reported)		
	Children (No age range reported)		

Abbreviations: FDA=Food and Drug administration; ESCMID=European Society of Clinical Microbiology and Infectious Diseases; IDSA=Infectious Diseases Society of America; PNA=postnatal age; GA=gestational age.
*Dutch label

FDA[4]		ESCMID[2]		IDSA[3]	
Prophylaxis	**Treatment**	**Prophylaxis**	**Treatment**	**Prophylaxis**	**Treatment**
3-12 mg/kg every 72 hours					
3-12 mg/kg every 24 hours					
		3-6 mg/kg twice weekly##		3-6 mg/kg twice weekly##	
			(Loading dose 25 mg/kg)# 12 mg/kg every 24 hours#		12 mg/kg every 24 hours
			(Loading dose 25 mg/kg)# 12 mg/kg (max. 400 mg) every 24 hours#		
6-12 mg/kg every (max. 600 mg) 24 hours#	(Loading dose 6-12 mg/kg, max. 600 mg)# 3-12 mg/kg (max. 600 mg) every 24 hours#	8-12 mg/kg (max. 400 mg) every 24 hours			12 mg/kg every 24 hours

#Fluconazole (loading) dose is dependent on type, severity and localization of the infection.
##Fluconazole prophylaxis is dependent on risk stratification strategy (incidence rate *Candida* infection and risk factors neonates)

Table 3. Non-compartmental analyses of fluconazole

Population	Dose	Formulation	Weight	N	SD, FD or MD		
						C_{max}	C_{min}
Premature neonates aged <24h after birth	6 mg/kg IV with a dose interval of 72h	IV	NR	12	FD day 1	Mean (range)* 5.5 mg/L (3.7-10.2) C_{max}	NR
			NR		MD day 7 day 13	Mean (range)* 12.8 mg/L (6.0-17.8) 10.0 mg/L (6.0-14.1) C_{max}	NR
Premature Infants <3 months of age	6 mg/kg daily	IV (N=2) and PO (N=6) (suspension)	NR	6	SD	median(range)* 9.6 mg/L (6.0-13.5) C_{max}	NR
Children with or without peritoneal dialysis (PD) after open heart surgery aged 2 weeks to 3 years	3 mg/kg daily	IV	Mean(STDV) 4.0 kg (1.1)	17	MD PD	Mean(STDV) 2.13 mg/L (0.99) C_{max}, day 1 3.86 mg/L (2.86) C_{max}, day 2 5.32 mg/L (4.06) C_{max}, day 3 4.60 mg/L (3.43) C_{max}, day 4	Mean(STDV) 1.66 mg/L (0.88) C_{trough}, day 1 2.23 mg/L (1.22) C_{trough}, day 2 3.17 mg/L (1.64) C_{trough}, day 3 2.60 mg/L (1.12) C_{trough}, day 4
			Mean(STDV) 4.4 kg (1.1)		MD Non-PD	Mean(STDV) 2.84 mg/L (0.83) C_{max}, day 1 5.43 mg/L (2.17) C_{max}, day 2 6.93 mg/L (3.89) C_{max}, day 3 6.23 mg/L (1.97) C_{max}, day 4	Mean(STDV) 2.03 mg/L (1.14) C_{trough}, day 1 3.06 mg/L (1.32) C_{trough}, day 2 4.00 mg/L (2.35) C_{trough}, day 3 4.15 mg/L (0.95) C_{trough}, day 4
Immunocompromised children(congenital disease, HIV, malignant disease or prematurity) aged 0.25 to 16 years	2, 3 or 8 mg/kg daily	IV and PO	NR	101[#]	NR 0.25-2 years 2-12 years ≥12 years 2 mg/kg IV	NR	NR
					0.25-2 years 2-12 years ≥12 years 2 mg/kg PO	NR	NR
					0.25-2 years 2-12 years ≥12 years 3 mg/kg IV	NR	NR
					0.25-2 years 2-12 years ≥12 years 3 mg/kg PO	NR	NR
					0.25-2 years 2-12 years ≥12 years 8 mg/kg IV	NR	NR
					0.25-2 years 2-12 years ≥12 years 8 mg/kg PO	NR	NR

Pharmacokinetic parameters					Reference
T_{max}	AUC	$T_{1/2}$	CL	V_d	
Mean (range) 2.2 h (0.2-6.6)	NR	Mean(range) 88.6 h (43.3-187.3)	Mean(range)* 0.011 L/h/kg (0.005-0.017)	Mean(range) 1.18 L/kg (1.05-1.48)	12
Mean (range) 1.6 h (0.25-6.3) 1.6 h (0.25-6.7)	NR	Mean(range) 67.5 h (30.8-130.8) 55.2 h (31.2-70.7)	Mean(range)* 0.020 L/h/kg (0.009-0.045) 0.031 L/h/kg (0.016-0.046)	Mean(range) 1.84 L/kg (0.70-5.71) 2.25 L/kg (1.49-3.68)	
NR	Median(range)* 412 mg*h/L (340-636) AUC_{inf}	NR	median(range)* 0.014 L/h/kg (0.007-0.017) CL/F	NR	13
NR	NR	Mean(STDV) 72.4 h (9.7)	Mean(STDV)* 0.018 L/h/kg (0.008) CL_{plasma} 0.014 L/h/kg (0.005) CL_{pd}(24h peritoneal clearance)	Mean(STDV) 1.39 L/kg (0.22)	14
NR	NR	Mean(STDV) 30.9 h (4.0)	Mean(STDV)* 0.025 L/h/kg (0.043) CL_{plasma} 0.014 L/h/kg (0.0032) $CL_{renal\ 24h}$	Mean(STDV) 1.07 L/kg (0.11)	
NR	Mean (STDV)* NR 73.7 mg*h/L (38.6) 92.2 mg*h/L** AUC_{inf}	Mean (STDV) 21.4 h (4.7) 22.7 h (9.8) 21.4 h (8.5)	NR	Mean (STDV) 0.95 L/kg (0.15) 0.95 L/kg (0.39) 0.70 L/kg (0.13)	15
NR	Mean (STDV)* 56.2 mg*h/L (12.0) 103.6 mg*h/L (29.7) 74.2 mg*h/L** AUC_{inf}				
NR	Mean (STDV)* 110.1 mg*h/L (20.2) NR NR AUC_{0-96}				
NR	Mean (STDV)* 51.4 mg*h/L** 62.8 mg*h/L (15.8) 52.8 mg*h/L** AUC_{0-48}				
NR	Mean (STDV)* NR 218.2 mg*h/L (77.1) 230.9 mg*h/L (94.2) AUC_{inf}				
NR	Mean (STDV)* NR 354.0 mg*h/L (223.6) 354.4 mg*h/L (127.9) AUC_{inf}				

Table 3. Continued

Population	Dose	Formulation	Weight	N	SD, FD or MD	C_{max}	C_{min}
Children with HIV aged 5 - 13 years	2 or 8 mg/kg	PO (suspension)	NR	9	SD 2 mg/kg 8 mg/kg 2 mg/kg 8 mg/kg	Median(range)* 2.95 mg/L (2.31–4.40) 10.3 mg/L (5.44-12.14) C_{max}	NR
Children with neoplastic disease 5-15 years old	2, 4, or 8 mg/ kg IV daily for 7 days	IV	Mean(range) 35.6 kg (16-60) 36.6 kg (25-64) 35.5 kg (18-55)	24	SD 2 mg/kg 4 mg/kg 8 mg/kg	Mean (SEM)* 3.9 mg/L (0.20) 6.4 mg/L (0.31) 9.5 mg/L (0.14) C_{max}	Mean (SEM)* 1.7 mg/L (0.09) 2.0 mg/L (0.13) 2.7 mg/L (0.14) C_{min}
			Mean(range) 36.9 kg (16-60) 36.8 kg (25-64) 38.6 kg (30-55)	17	MD 2 mg/kg 4 mg/kg 8 mg/kg	Mean(SEM)* 5.4 mg/L (0.39) 10.5 mg/L (0.69) 14.3 mg/L (0.35) C_{max}	Mean(SEM)* 2.5 mg/L (0.30) 3.2 mg/L (0.55) 5.5 mg/L (0.29) C_{min}
			NR	26	Overall	NR	NR

Abbreviations: IV=intravenous; PO=’per os’; N=total patients; SD=single dose; FD=first dose; MD=multiple dose; C_{max}=maximal serum concentration; C_{min}=minimal serum concentration; C_{trough}=trough concentration; T_{max}=time to reach C_{max}; AUC=area under the curve; $t_{1/2}$=elimination half-life; CL=clearance; V_d=volume of distribution; F=bioavailability; NR=not reported; HIV= Human immunodeficiency virus infection; PD=peritoneal dialysis; STDV=standard deviation; SEM=standard error of the mean.

Pharmacokinetic parameters					Reference
T_{max}	AUC	$T_{1/2}$	CL	V_d	
Median(range)* 2.0 h (0.5-2.0) 1.0 h (1.0-4.0)	Median(range)* 48.3 mg*h/L (40.6-58.2) 205.9 mg*h/L (133.9-241.9) AUC_{0-24} Median(range)* 97.8 mg*h/L (84.9-135.9) 413.5 mg*h/L (330.2-684.3) AUC_{inf}	Median(range)* 27.1 h (19.8-34.9) 32.1 h (25.6-42.3)	NR	NR	16
NR	Mean(SEM)* 89 mg*h/L (14) 120 mg*h/L (22) 186 mg*h/L (16) AUC_{inf}	Mean(SEM) 20.3 h (2.7) 15.5 h (1.8) 15.8 h (1.6)	Mean(SEM)* 0.020 L/h/kg (0.0024) 0.037 L/h/kg (0.0048) 0.049 L/h/kg (0.0063)	Mean(SEM) 0.60 L/kg (0.05) 0.82 L/kg (0.09) 1.06 L/kg (0.08)	17
NR	Mean(SEM)* 76 mg*h/L (14) 110 mg*h/L (24) 201 mg*h/L (16) AUC_{0-24}	Mean(SEM) 20.7 h (2.9) 17.1 h (2.9) 16.9 h (1.8)	Mean(SEM)* 0.027 L/h/kg (0.0046) 0.037 L/h/kg (0.0051) 0.030 L/h/kg (0.0034)	Mean(SEM) 0.88 L/kg (0.05) 0.93 L/kg (0.11) 0.74 L/kg (0.08)	
NR	NR	Mean(SEM) 17.4 h (1.1)	Mean(SEM)* 0.035 L/h/kg (0.0025)	Mean(SEM) 0.86 L/kg (0.4)	

*Values recalculated/adjusted from original paper to create uniformity of units (when individual values were reported the median was calculated from these values).
**Data only available from one patient.
#The study of Brammer *et al*. pooled data of 113 patients from previous studies. The 12 patients of the study of Saxen *et al*. were only reported and not analysed in this pooled study and therefore not mentioned here (N=101). The study of Lee *et al*. was also included in this pooled study but the results of the 4 mg/kg regimen are not reported.

Table 4. Population pharmacokinetic estimates of fluconazole

Population	Dose	Formulation	Weight	N	SD, FD or MD	Pharmacokinetic parameters
						AUC
Preterm neonates at risk for invasive candidiasis with a median PNA of 3 days.	3 mg/kg with a dose interval of 72h	IV and PO (orogastric tube)	Median(range) 1.1 kg (0.9 to 1.3)	75	MD	NR
Preterm neonates <750 grams with a median PNA of 23 days.	6 mg/kg twice weekly	IV and PO (suspension)	Median(range)** 0.71 kg (0.35-2.7)	141	MD	NR
Preterm and term neonates and infants with suspected or proven candidiasis and a 23- to 40-week gestation and a mean PNA of 13.5 days.	<30 weeks CGA: loading dose 25 mg/kg, maintenance dose 12 mg/kg ≥30 weeks CGA: loading dose 25 mg/kg, maintenance dose 20 mg/kg	IV	Median(range)** 1.26 kg (0.750-4.255)	18	MD	Median(95% CI) 490.9 mg*h/L (406.2 – 571.9) AUC_{0-24}, day 1 898.2 mg*h/L (503.4 -1445.7) AUC_{0-24}, SS
Neonates and infants with oral candidiasis or at risk for invasive fungal disease aged between 9 days and 4.4 months.	3 mg/kg	IV	Mean(SEM) 4.1 kg (0.2)	14	SD	Mean(SEM)** 90.2 mg*h/L (9.0) AUC_{inf}
Preterm and term infants at risk for invasive candidiasis with a 23- to 42-week gestation and aged <120 days.	Dosing ranged from 3 to 12 mg/kg/dose	IV	Median(range)** 1.020 kg (0.451-7.125)	55	MD	NR
Hospitalized neonates and infants at risk for invasive fungal disease and a median gestation age of 37 weeks aged <60 days.	Loading dose (25 mg/kg IV), followed by maintenance therapy (12 mg/kg daily)	IV	NR	8	MD	Median(IQR) 479 mg*h/L (347-496)AUC_{0-24}
Infants supported with ECMO, with a 23- to 41-week gestation and aged <120 days of age.	IV Prophylaxis: 25 mg/kg once a week Followed by IV Treatment: 12 mg/kg daily in patients with suspected or known fungal disease ##	IV	Median(IQR) 3.2 kg (2.6 – 3.4)	10	FD MD	Median(IQR) 322 mg*h/L (307-343)AUC_{0-24} Median(IQR) 352 mg*h/L (344-399)AUC_{0-24}
See reference [23], [24] and [25]. From study [24] only patients with a GA of ≥36 weeks were included.	See reference [24], [24] and [25]	IV	Median(range) 3.4 kg (1.9-77)	40 (21 with ECMO)##	FD and MD	NR
Immunocompromised haemato-oncology patients aged 1.8 to 15.9 years	SD: 6 mg/kg IV Followed by MD: 3 mg/kg PO	IV and PO (tablets)	Mean(STDV) 31.6 kg (25.9)	10	SD and MD	NR

Abbreviations: PNA=postnatal age; CGA; corrected gestational age; IV=intravenous; PO='per os' (oral administration); N=total patients; SD=single dose; FD=first dose; MD=multiple dose; AUC=area under the curve; t1/2=elimination half-life; CL=clearance; V1=volume of distribution in the central compartment; Q=intercompartmental clearance; V2=volume of distribution of the peripheral compartment; V_d = volume of distribution; $V_{d,SS}$ = volume of distribution at steady state; K_a= rate of oral bioavailability; F=bioavailability; NR=not reported; RSE=relative standard error; SEE=standard error of estimate; CI=confidence interval; IQR=interquartile range;SS=steady state; HIV= Human immunodeficiency virus infection; PD=peritoneal dialysis; STDV=standard deviation; SEM=standard error of the mean; ECMO=extracorporeal membrane oxygenation.

$T_{1/2}$	CL	V1	Q	V2	K_a	F	Reference
NR	0.0197 × (WT/1.00)$^{0.746}$ × (eGFR/25.0)$^{0.463}$	1.04 × (WT/1.00)	NR	NR	Estimate(RSE%) 0.538 1/h (18.5)	Estimate(RSE%) 0.909 (7.03)	20
NR	0.0127 × (SCR/0.8)$^{0.41}$ × (PMA/28)$^{2.05}$*	1.00***	NR	NR	Point estimate(SEE) 0.96 1/h (0.25)	Point estimate(SEE) 1.00 (0.065)	21
Median(95% CI) 40.9 h (16.2 - 78.4)	Median(95% CI) 0.015 L/h/kg (0.008 - 0.039)	Median(95% CI) 0.913 L/kg (0.913 - 0.913)	NR	NR	NR	NR	22
Mean(STDV) 22.5 h (2.2)	Mean(SEM)*** 0.0378 L/h/kg (0.0036)	Mean(SEM) 1.17 L/kg (0.14)	NR	NR		NR	27
NR	0.015 × (WT/1.00)$^{0.75}$ × (BGA/26)$^{1.739}$ × (PNA/2)$^{0.237}$ × (SCRT/1)$^{(-4.899)(CR)}$****	1.024 × (WT/1.00)^{1}	NR	NR	NR	NR	23
Median(IQR) 56 h (26-80)	Median(IQR)*** 0.016 L/h/kg (0.013-0.021)	Median(IQR)*** 1.051 L/kg (0.858-1.461)	NR	NR	NR	NR	24
Median(IQR) 60 h (47-76)	Median(IQR)***# 0.017 L/h/kg (0.014-0.022)	Median (IQR)# 1.5 L/kg (1.3-1.7)	NR	NR	NR	NR	25
Median(IQR) 56 h (37-92)	Median(IQR)***# 0.022 L/h/kg (0.011-0.033)	Median(IQR)# 1.9 L/kg (1.4-2.2)	NR	NR	NR	NR	
NR	0.019 × WT × (SCR/0.4)$^{-0.29}$	0.93 × WT × 1.4^{ECMO*****}	NR	NR	NR	NR	26
Mean(STDV) 15.63 h (3.21)	Mean(STDV)*** 0.0380 L/h/kg (0.0112)	Mean(STDV) 0.562 L/kg (0.106)V_d Mean(STDV) 0.770 L/kg (0.125)$V_{d,SS}$	NR	NR	Mean(STDV) 3.76 1/h (4.88)	Mean(STDV) 0.92 (0.09)	28

*Fixed or estimated value of exponent used for allometric scaling of volume of distribution was not reported.
**Values recalculated/adjusted from original paper to create uniformity of units.
***Unclear how WT was standardized in this equation.
****WT normalized to 1 kg/week (1 week) and CR (creatinine value) = 1 if SCRT > 1 mg/dl, CR = 0 if SCRT ≤ 1 mg/dl.
*****ECMO = 1 or 0.
#Only one patient received fluconazole treatment.
##Number of ECMO patients reported in this pooled study do not add up with the number of ECMO patients in the individual studies.

Table 5. Pharmacokinetic models of fluconazole

Population	Subjects N	Samples N	Programme	Covariates tested
Preterm neonates at risk for invasive candidiasis with a median PNA of 3 days.	75	303	NONMEM	WT, HT, eGFR, SCR, GA, PMA, PNA, ALT, AST, BUN
Preterm neonates <750 grams at risk for invasive candidiasis with a median PNA of 23 days.	141	604	NONMEM	WT, PNA, GA, PMA SCR, ALB, race, ethnicity, intubation status, mode of delivery (Cesarean section or vaginal).
Preterm and term neonates and infants with suspected or proven candidiasis and a mean PNA range 13.5 days.	18	82	NONMEM	WT, PMA
Neonates and Infants aged between 9 days and 4.4 months with oral candidiasis or at risk for invasive fungal disease	14	NR	TOPFIT	Age
Preterm and term neonates and infants with a 23- to 42-week gestation and aged <120 days	55	357	NONMEM	WT, BGA, PNA, PMA (defined as BGA plus PNA in weeks), and SCR
Hospitalized neonates and infants at risk for invasive fungal disease and <60 days of age.	8	57	WinNonLin	SCR (linear regression analysis)
Infants supported with ECMO with a 23- to 41-week gestation and aged <120 days	10	62 First dose 47 Multiple dose	WinNonLin	SCR, ECMO (linear regression analysis)
See references [23–25]. From study [24] only patients with a GA of ≥36 weeks were included	40 of which 21 with ECMO	360	NONMEM	WT, ECMO support, volume of blood r equired to prime the ECMO circuit, ratio of blood prime volume to the e stimated native blood volume of the child, hemofiltration, use of CVVHD, SCR, ALB, AST, ALT, PNA, sex, race
Immunocompromised haemato-oncology patients aged 1.8 to 15.9 years	10	NR	NONMEM	Age, WT, HT, BSA, creatinine clearance (linear regression analysis)

Abbreviations: N=total; PO=’per os’; IV=intravenously; Cl=clearance; V1=volume of distribution in the central compartment; V2=volume of distribution in the peripheral compartment; Q=intercompartmental clearance, eGFR =estimated glomerular filtration rate; PNA=postnatal age; ECMO: extracorporeal membrane oxygenation; WT=weight; HT=height; GA=gestational age; BGA=gestational age at birth; PMA=postmenstrual age; BGA=gestational age at birth; SCR=serum creatinine; ALB=albumin; AST= aspartate aminotransferase; ALT= Alanine aminotransferase; BUN=blood urea nitrogen level; BSA=body surface area; CVVHD= continuous venovenous hemodialysis; SD= single dose; MD=multiple dose.

Compartments	PO/IV	Covariates in final model					Reference
		CL	V1	Q	V2	T1/2	
1, with first-order absorption	IV and PO	eGFR with estimated exponent, allometrically scaled WT with estimated exponent. Both normalised to a standard individual.	Allometrically scaled WT with fixed exponent, normalised to a standard individual.	NR	NR	NR	[20]
1, with first-order absorption	IV and PO	Allometrically scaled WT with a fixed exponent of 0.75,SCR, PMA(as function of GA and PNA). All normalised to a standard individual.	Allometrically scaled WT with a fixed exponent of 1 and normalised to a standard individual.	NR	NR	NR	[21]
1	IV	WT*	NR	NR	NR	NR	[22]
1	IV	NR	Age	NR	NR	Age	[27]
1	IV	Allometrically scaled WT with a fixed exponent of 0.75, BGA, PNA and SCR. All normalised to a standard individual.	Allometrically scaled weight with a fixed exponent of 1 and normalised to a standard individual	NR	NR	NR	[23]
1	IV	SCR	NR	NR	NR	NR	[24]
1	IV	SCR	ECMO	NR	NR	NR	[25]
1	IV	Exponent for creatinine, WT	Coefficient for ECMO, WT	NR	NR	NR	[26]
2, with first-order absorption	IV and PO	BSA	WT**	NR	NR	NR	[28]

*WT is included as covariate on fluconazole CL, however the covariate equation was not reported.
**V_{dss} was best correlated with BSA

Table 6. Non-compartmental analyses of itraconazole

Population	Dose	Formulation	Weight	N	SD, FD or MD	
						C_{max}
Children at risk for IFD aged 0.5 to 17 years	2.5 mg/kg	IV	Mean(STDV) 31.1kg (22.7)	33	SD	ITZ* Mean(STDV)
					0.5-2 years	0.827 mg/L (0.859)
					>2-6 years	1.553 mg/L (0.918)
					>6-12 years	0.785 mg/L (0.301)
					>12-16 years	0.806 mg/L (0.381)
					Overall	1.015 mg/L (0.692)
						C_{max}
						H-ITZ* Mean (STDV)
					0.5-2 years	0.265 mg/L (0.257)
					>2-6 years	0.299 mg/L (0.162)
					>6-12 years	0.277 mg/L (0.104)
					>12-16 years	0.321 mg/L (0.093)
					Overall	0.293 mg/L (0.133)
						C_{max}
HSCT patients aged 0.9 to 23 years, for PK part patients aged 9.4-14.8 years.	Prophylaxis: 2.5 mg/kg every 12 h for 2 days. Followed by treatment with 5 mg/kg every 12 h for 2 days, and a maintenance dose of 5 mg/kg daily	Prophylaxis: PO (solution) Treatment: IV	Mean# 29 kg	6	MD (after third IV dose)	ITZ* Mean(STDV) 4.429 mg/L (1.072) $C_{max,SS}$
						H-ITZ* Mean(STDV) 3.778 mg/L (0.722) $C_{max,SS}$
CF patients <16 years	2.5 mg/kg every 12h for 14 days	PO (solution)	Median(range) 16.6 kg/m2 (15–19.7) BMI	5	FD day 1	ITZ* Mean(STDV) 0.133 mg/L (0,135) C_{max}
						H-ITZ* Mean(STDV) 0.230 mg/ml (0.141) C_{max}
					MD day 14	ITZ* Mean(STDV) 0.404 mg/mL (0.268) C_{max}
						H-ITZ* Mean(STDV) 0.550 mg/mL (0.240) C_{max}

Pharmacokinetic parameters						Reference
C	**T_{max}**	**AUC**	**$T_{1/2}$**	**CL**	**V_d**	
NR	NR	ITZ* Mean(STDV) 2.121 mg*h/L (1.231) 9.510 mg*h/L (1.1316) 3.765 mg*h/L (1.711) 2.669 mg*h/L (1.076) 4.922 mg*h/L (6.784) AUC_{0-24}	ITZ Mean(STDV) 13.3 h (4.15) 14.0 h (8.05) 17.2 h (7.94) 29.0 h (15.6) 20.2 h(12.8)	ITZ* Mean(STDV) 1.143 L/h/kg (0.513) 0.529 L/h/kg (0.611) 0.621 L/h/kg (0.340) 0.777 L/h/kg (0.455) 0.7028 L/h/kg (0.4994)	ITZ* Mean(STDV) 23.6 L/kg (15.2) 8.3 L/kg (7.1) 13.9 L/kg (5.8) 28.5 L/kg (15.9) 18.5 L/kg (14.2)	39
NR	NR	H-ITZ* Mean(STDV) 4.155 mg*h/L (3.657) 4.249 mg*h/L (4.103) 4.166 mg*h/L (2.036) 3.133 mg*h/L (1.789) 3.811 mg*h/L (2.794) AUC_{0-24}	H-ITZ Mean(STDV) 16.6 h (3.07) 12.7 h (7.40) 14.3 h (6.76) 12.3 h (8.06) 13.3 h (7.0)	NR	NR	
NR	NR	ITZ* Mean(STDV) 42.837 mg*h/L (24.746) $AUC_{0-24,SS}$	ITZ Mean(STDV) 39.5 h (33.5)	ITZ* Mean(STDV) 0.1313 L/h/kg (0.05652) CL_{SS}	ITZ* Mean(STDV) 6.959 L/kg (6.897) V_{SS}	40
NR	H-ITZ Median(range) 4 h (1.0-7.6)	H-ITZ* Mean(STDV) 63.094 mg*h/L(19255) $AUC_{0-24\,SS}$	H-ITZ Mean(STDV) 51.0 h(17.9)	H-ITZ* Mean(STDV) 0.07969 L/h/kg (0.02662) CL_{SS}	H-ITZ* Mean(STDV) 5.659 L/kg (2.341) V_{SS}	
NR	NR	ITZ* Mean(STDV) 0.433 mg*h/L (358) AUC_{0-12}	NR	NR	NR	41
NR	NR	H-ITZ* Mean(STDV) 1.168 mg*h/L (707) AUC_{0-12}	NR	NR	NR	
ITZ* Mean(STDV) 0.119 mg/L (0.0834) C_{min} Mean(STDV) 0.191 mg/L (0.110) Css,av		ITZ* Mean(STDV) 2.298 mg*h/LL (1.322) AUC_{0-12}	NR	NR	NR	
H-ITZ* Mean(STDV) 0.276 mg/L (0161) C_{min} Mean(STDV) 0.400 ng/ml (0.216) $C_{ss,av}$		H-ITZ* Mean(STDV) 4.792 mg*h/L (2594) AUC_{0-12}	NR	NR	NR	

Table 6. Continued

Population	Dose	Formulation	Weight	N	SD, FD or MD	
						C_{max}
Infants and children aged 0.5 to 12 years with haematological malignancy or liver transplantation with mucosal fungal infection or at risk for IFD	5 mg/kg of body weight once daily for 2 weeks	PO (oral solution)	Mean(STDV) 16.9 kg (1.7)	26	FD day 1 0.5-2 years 2-5 years 5-12 years	ITZ* Mean(STDV) 0.138 mg/L (0.091) 0.314 mg/L (0.105) 0.298 mg/L (0.292) C_{max}
						H-ITZ* Mean(STDV)
					0.5-2 years 2-5 years 5-12 years	0.179 mg/L (0.101) 0.493 mg/L (0.106) 0.447 mg/L (0.365) C_{max}
					MD day 14 0.5-2 years 2-5 years 5-12 years	ITZ* Mean(STDV) 0.571 mg/L (0.416) 0.534 mg/L (0.431) 0.631 mg/L (0.358) C_{max}
						H-ITZ* Mean(STDV)
					0.5-2 years 2-5 years 5-12 years	0.690 mg/L (0.445) 0.687 mg/L (0.419) 0.699 mg/L (0.234) C_{max}
Cancer patients at risk for IFD aged 2-12 years	2.5 mg/kg PO every 12h	PO (oral solution)	NR	17	MD	ITZ* Mean(STDV)
					2-5 years 6-12 years	0.599 mg/mL (0.231) 1.090 mg/L (0.383) $C_{max\ 4h}$, day 7
						ITZ* Mean(STDV)
					2-5 years 6-12 years	1.024 mg/L (0.351) 1.524 mg/L (0.770) $C_{max\ 4h}$, day 15
					2-5 years 6-12 years	
					MD	H-ITZ* Mean (STDV)
					2-5 years 6-12 years	1.008 mg/L (0.341) 1.658 mg/L (0.426) $C_{max\ 4h}$, day 7
						H-ITZ* Mean(STDV)
					2-5 years 6-12 years	1.358 mg/L (0.373) 2.180 mg/L (0.753) $C_{max\ 4h}$, day 15
					2-5 years 6-12 years	

Pharmacokinetic parameters						Reference
C	**T_{max}**	**AUC**	**$T_{1/2}$**	**CL**	**V_d**	
NR	NR	ITZ* Mean(STDV) 1.340 mg*h/L (0.780) 2.740 mg*h/L (1.080) 2.010 mg*h/L (1.580) AUC_{0-24}	NR	NR	NR	42
NR	NR	H-ITZ* Mean(STDV) 2.340 mg*h/L (1.490) 6.730 mg*h/L (1.950) 4.920 mg*h/L (4.390) AUC_{0-24}	NR	NR	NR	
ITZ* Mean(STDV) 0.159 ng/ml (0.218) 0.179 ng/ml (0.101) 0.223 ng/ml (0.145) predose concentration		ITZ* Mean(STDV) 6.930 mg*h/L (5.830) 7.330 mg*h/L (5.420) 8.770 mg*h/L (5.050) AUC_{0-24}	ITZ Mean(STDV) 47.4 h (55.0) 30.6 h (25.3) 28.3 h (9.6) $T_{1/2term}$	NR	NR	
H-ITZ* Mean(STDV) 0.308 mg/L (0.436) 0.487 mg/L (0.314) 0.437 mg/L (0.246) predose concentration		H-ITZ* Mean(STDV) 13.200 mg*h/L (11.400) 13.400 mg*h/L (9.110) 13.450 mg*h/L (7.190) AUC_{0-24}	H-ITZ Mean(STDV) 18.0 h (18.1) 17.1 h (14.5) 17.9 h (8.7) $T_{1/2term}$	NR	NR	
ITZ* Mean(STDV) 0.439 mg/L (0.255) 0.674 mg/L (0.285) $C_{min\ 12h}$, day 7	ITZ Mean(STDV) 13 days (4) 12 days (6) T_{Css}	ITZ* Mean(STDV) 16.128 mg*h/L (130) 20.496 mg*h/L (302) $AUC_{min/d}$	NR	NR	NR	43
ITZ* Mean(STDV) 0.711 mg/L (0.251) 1.072 mg/L (0.408) $C_{min\ 12h}$, day 15						
ITZ* Mean(STDV) 0.877 mg/L (0.248) 1.085 mg/L (0.329) C_{ssmin}						
H-TZ* Mean (STDV) 0.915 mg/L (0.396) 1.427 mg/L (0.449) $C_{min\ 12h}$, day 7	H-ITZ Mean (STDV) 14 days (8) 11 days (5) T_{Css}	H-ITZ* Mean(STDV) 28.488 mg*h/L (0.223) 36.840 mg*h/L (0.419) $AUC_{min/d}$	NR	NR	NR	
H-ITZ* Mean(STDV) 1.275 mg/L (0.322) 1.964 mg/L (0.562) $C_{min\ 12h}$, day 7						
H-ITZ* Mean(STDV) 1.536 mg/L (0.334) 1.919 mg/L (0.535) C_{ssmin}						

Table 6. Continued

Population	Dose	Formulation	Weight	N	SD, FD or MD	
						C_{max}
HIV-infected patients aged 5 to 18 years with oropharyngeal candidiasis	2.5 mg/kg every 12 or 24h	PO(oral solution)	NR	26	FD	ITZ* Mean(STDV) 0.420 mg/L (0.06) C_{max}
						H-ITZ* Mean(STDV) 0.319 mg/L (0.04) Cmax
					MD QD	ITZ* Mean(STDV) 0.623 mg/L (0.14) C_{max}
					BID	Mean(STDV) 1.340 mg/L (0.22) C_{max}
					MD QD	H-ITZ* Mean(STDV) 0.552 mg/L (0.08) C_{max}
					BID	Mean(STDV) 1.170 mg/L (0.18) C_{max}

Abbreviations: IFD= invasive fungal disease; HIV= human immunodeficiency virus; HSCT= Haematopoietic stem cell transplantation; IV=intravenous; PO='per os' (oral administration); N=total patients; SD=single dose; FD= first dose; MD=multiple dose; QD=once daily; BID=twice daily; SS=steady state; C_{max}=maximum serum concentration; C_{min}=minimal serum concentration; $C_{ss,av}$=average steady-state plasma concentration ; C_{avg}=average serum concentration; T_{max}=time to reach C_{max}; T_{Css} =Time to reach $C_{ss,min}$; AUC=area under the curve; $AUC_{min/d}$ = AUC_{min} standardized to a day; $T_{1/2}$=elimination half-life; CL=clearance; V_d=volume of distribution; F=bioavailability; NR=not reported; STDV=standard deviation; ITZ=itraconazole; H-ITZ=hydroxy-itraconazole; IQR=interquartile range.

Pharmacokinetic parameters						Reference
C	**T_{max}**	**AUC**	**$T_{1/2}$**	**CL**	**V_d**	
NR	ITZ Mean(STDV) 2.35 h (0.37) T_{max}	ITZ* Mean(STDV) 3.720 mg*h/L (0.65) AUC_{0-24}	ITZ Mean(STDV) 25.6 h (5.7) $T_{1/2}$	ITZ Mean(STDV) 0.660 L/h/kg (0.17)	ITZ Mean(STDV) 18.90 L/kg (5.3) $V_{d,ss}$	44
NR	H-ITZ Mean(STDV) 7.14 h (1.69) T_{max}	H-ITZ* Mean(STDV) 5.240 mg*h/L (0.81) AUC_{0-24}	H-ITZ Mean(STDV) 26.8 h (4.0) $T_{1/2}$	H-ITZ Mean(STDV) 0.339 L/h/kg (0.05)	NR	
ITZ* Mean(STDV) 0.192 mg/L (0.06) C_{min}	ITZ Mean(STDV) 1.9 h (0.3)	ITZ* Mean(STDV) 7.05 mg*h/L (2.06) AUC_{0-tau} 7.05 mg*h/L (2.06) AUC_{0-24}	ITZ Mean(STDV) 58.9 h (13.1) $T_{1/2}$	ITZ Mean(STDV) 0.601 L/h/kg (0.26)	ITZ Mean(STDV) 15.52 L/kg (4.47) $V_{d,ss}$	
Mean(STDV) 0.782 mg/L (0.19) C_{min}	Mean(STDV) 1.8 h (0.3) T_{max}	Mean(STDV) 11.52 mg*h/L (2.19) AUC_{0-tau} 23.04 mg*h/L (4.39) AUC_{0-24}	Mean(STDV) 104.2 h (28.3) $T_{1/2}$	Mean(STDV) 0.073 L/h/kg (0.029)	Mean(STDV) 5.11 L/kg (1.28) $V_{d,ss}$	
H-ITZ* Mean(STDV) 0.383 mg/L (0.10) C_{min}	H-ITZ Mean(STDV) 5.9 h (1.5)	H-ITZ* Mean(STDV) 11.18 mg*h/L (2.82) AUC_{0-tau} 11.18 mg*h/L (2.82) AUC_{0-24}	H-ITZ Mean(STDV) 55.6 h (21.3) $T_{1/2}$	H-ITZ Mean(STDV) 0.160 L/h/kg (0.05)	NR	
Mean(STDV) 0.997 mg/L (0.15) C_{min}	Mean(STDV) 14.7 h (6.9) T_{max}	Mean(STDV) 11.89 mg*h/L (2.06) AUC_{0-tau} 23.75 mg*h/L (4.11) AUC_{0-24}	Mean(STDV) 168.8 h (81.3) $T_{1/2}$	Mean(STDV) 0.047 L/h/kg (0.01)		

*Values recalculated/adjusted from original paper to create uniformity of units.
#Error not mentioned.

Table 7. Population pharmacokinetic estimates of itraconazole

Population	Dose	Formulation	Weight	N	SD, FD or MD	Pharmacokinetic parameters			
						AUC	$T_{1/2}$	T_{lag}	CL
Children at risk for IFD aged 6 months to 17 years	2.5 mg/kg	IV	Mean(STDV) 31.1 kg (22.7)	33	SD	NR	NR	NR	ITZ*# Estimated value 16.9 L/h
Paediatric CF patients and BMT patients aged 0.4 to 18 years. (including 5 adults aged 19–30 years)	Median (range) 5.4 mg/kg (1.5–12.5) daily dose	PO (capsule/ solution)	Median(range) 29.3 kg (6.8–83.5)	49 (incl. 5 adults)	MD	NR	NR	Mean(RSE%) 19.1 min (3.3)	ITZ** Mean(RSE%) 35.5 L/h (13.8) H-ITZ Mean(RSE%) 10.6 L/h (14.1)

Abbreviations: N = number of patients; SD= single dose, FD=first dose; MD = multiple dose, AUC = area under the curve; $T_{1/2}$ = elimination half-life; T_{lag} = lagtime; CL = clearance; V1= volume of distribution (central compartment 1); Q1 = intercompartmental clearance(compartment 1-2); V2 = volume of distribution (peripheral compartment 2), Q2 = intercompartmental clearance (compartment 1-3) ; V3 = volume of distribution (peripheral compartment 3; K_a = rate of oral bioavailability; F = bioavailability; IFD = invasive fungal disease; (STDV) = standard error; ITZ = itraconazole;

V1	Q1	V2	Q2	V3	K_a	F	Reference
ITZ*# Estimated value 63.8 L	ITZ*# Estimated value 30.2 L/h	ITZ*# Estimated value 134 L	ITZ*# Estimated value 9.57 L/h	ITZ*# Estimated value 88.1 L	NR	NR	39
ITZ** Mean(RSE%) 627.0 L (27.3)	NR	NR	NR	NR	Mean(RSE%) 0.09 1/h (21.7) Capsule	Mean(RSE%) 0.55 (12.7) $F_{relative}$***	45
H-ITZ Mean(RSE%) 5.29 L (4.1)	NR	NR	NR	NR	Mean (RSE%) 0.96 1/h (67.4) Solution		

H-ITZ = hydroxy-itraconazole; NR = not reported; CF = cystic fibrosis; BMT = bone marrow transplantation; RSE = relative standard error.
*Values scaled to a body weight of 30 kg.
**Values scaled to a body weight of 70 kg.
***Relative bioavailability of capsules compared to solution.
#Error was not reported.

Table 8. Pharmacokinetic models of itraconazole

Population	Subjects N	Samples N	Programme	Covariates tested	Compartments	PO/IV
Children at risk for IFD (6 months to 16 years)	33	NR	NONMEM	WT	3, with first order elimination	IV
Paediatric patients with CF and BMT aged 0.4 to 18 years. (incl. 5 adults aged 19–30 years)	49 (29 CF of which 5 adults and 20 BMT)	227	NONMEM	total WT, lean WT, age, disease, and effect of acidic beverage and food intake, sex, disease category	1-compartment with first order absorption for ITZ and first order elimination to H-ITZ and a 1-compartment with first order elimination pathway for H-ITZ	PO (capsules and solution)

Abbreviations: N = number of patients; CL = clearance; V1= volume of distribution (central compartment 1); Q1 = intercompartmental clearance(compartment 1-2); V2 = volume of distribution (peripheral compartment 2), Q2 = intercompartmental clearance (compartment 1-3) ; V3 = volume of distribution (peripheral compartment 3; K_a = rate of oral bioavailability; F = bioavailability; WT=bodyweight; IFD = invasive fungal disease; (STDV) = standard deviation; ITZ = itraconazole; H-ITZ = hydroxy-itraconazole; NR = not reported; CF = cystic fibrosis; BMT = bone marrow transplantation.

Covariates in final model								Reference
CL	**V1**	**Q1**	**V2**	**Q2**	**V3**	**F**	**K_a**	
WT normalised to 30 kg	WT normalised to 30 kg	WT normalised to 30 kg	WT normalised to 30 kg	WT normalised to 30 kg	WT normalised to 30 kg	NR	NR	39*
ITZ Allometrically scaled WT normalised to 70 kg**	ITZ Allometrically scaled WT normalised to 70 kg**	ITZ NR	ITZ NR	ITZ NR	ITZ NR	ITZ NR	ITZ NR	45
H-ITZ NR	H-ITZ NR	H-ITZ NR	H-ITZ NR	H-ITZ NR	H-ITZ NR	H-ITZ NR	H-ITZ NR	

*WT is included as covariate on itraconazole parameters, however the covariate equation was not reported.
**Values of exponents used for allometric scaling are not reported.

Table 9. Non-compartmental analyses of voriconazole

Population	Dose	Formulation	Weight	N	SD, FD or MD		
						C_{max}	C_{min}
Haemato-oncology or HSCT paediatric patients aged 2 to <12 years.	7 mg/kg IV every 12h for 7 days followed by 200 mg PO every 12h for 6.5 days.	IV and PO	Median(range) 18.9 kg (10.8–54.5)	40	FD/MD	Median(range)	Median(range)
					Day 1 IV	1.99 µg/ml (0.90-6.68) C_{max}	NR
					Day 7 IV	4.49 µg/ml (1.48-15.4) $C_{max\ SS}$	0.61 µg/ml (0.06-10.9) $C_{min\ SS}$
					Day 7 PO	4.11 µg/ml (0.51-18.0) $C_{max\ SS}$	0.49 µg/ml (0.04-128) $C_{min\ SS}$
Haemato-oncology paediatric patients aged 2 to <12 years	Group A: 7 mg/kg IV every 12h.	IV	Mean(range) 24.2 kg (13–41)	12 (9 in group A and 3 in group B)	MD	Geometric mean (range)	Geometric mean(range)
	Group B: 6 mg/kg IV every 12h, followed by a maintenance dose of 5 mg/kg IV every 12h.				Day 3 Group A	11.4 µg/ml (2.9–19.2)	4.1 µg/ml (0.4-8.9) C_{avg}
					Group B	5.8 µg/ml (2.4-17.2)	2.2 µg/ml (1.1-3.5) C_{avg}
Haemato-oncology, BMT and HSCT paediatric patients aged 2 to <12 years.	Cohort 1 Day 1: 6 mg/kg IV every 12h; Day 2-4: 4 mg/kg IV every 12h; Day 5-8: 6 mg/kg IV every 12h.; Day 9-11: 4 mg/kg PO every 12h; From day 12: 4mg/kg PO every 12h.	IV and PO	Mean(range) Cohort 1 24.3 kg (13.0–54.9) Cohort 2 20.8 kg (10.8–37.6)	48	Cohort 1 MD	Geometric mean(CV%)*	NR
					2-5 years 4 mg/kg IV 6 mg/kg IV 4 mg/kg PO	3.352 µg/ml (71) 4.690 µg/ml (111) 0.956 µg/ml (85)	
					6-11years 4 mg/kg IV 6 mg/kg IV 4 mg/kg PO	3.067 µg/ml (64) 4.009 µg/ml (88) 1.555 µg/ml (54)	
					2-11years 4 mg/kg IV 6 mg/kg IV 4 mg/kg PO	3.212 µg/ml (67) 4.353 µg/ml (103) 1.178 µg/ml (70)	
					Cohort 2 MD	Geometric mean(CV%)*	NR
	Cohort 2 Day 1: 6 mg/kg IV every 12h; Day 2-4: 6 mg/kg IV every 12h; Day 5-8: 8 mg/kg IV every 12h; Day 9-11: 6 mg/kg PO every 12h; From day 12: 6 mg/kg PO every 12h.				2-5 years 6 mg/kg IV 8 mg/kg IV 6 mg/kg PO	4.609 µg/ml (93) 4.804 µg/ml (83) 1.433 µg/ml (66)	
					6-11 years 6 mg/kg IV 8 mg/kg IV 6 mg/kg PO	3.986 µg/ml (67) 6.924 µg/ml (123) 2.213 µg/ml (49)	
					2-11 years 6 mg/kg IV 8 mg/kg IV 6 mg/kg PO	4.286 µg/ml (85) 5.767 µg/ml (121) 1.762 µg/ml (57)	

Pharmacokinetic parameters						Reference
T_{max}	AUC	$T_{1/2}$	CL	V_d	F	
Median(range)	Median(range)	NR	NR	NR	NR	[51]
2.30 h(0.72-4.08)	7.00 µg*h/ml (2.43-36.6) AUC_{0-12}					
2.30 h (1.00-4.07) $T_{max\ SS}$	21.8 µg*h/ml (5.02-162) AUC_{0-12SS}					
1.07 h (0.73-8.03) $T_{max\ SS}$	20.1 µg*h/ml (1.70-203) AUC_{0-12SS}					
Geometric mean (range)	Geometric mean (range)	Geometric mean (range)	Geometric mean (range)	Geometric mean (range) 1852 ml/kg (953–3311)	NR	[53]
1.1 h (1.0–1.1)	49.3 µg*h/ml (4.7–106.6) AUC_{0-12}	10.9 h (3.1–29.2)	141.9 ml/h/kg (65.7–1483.1) CL_{SS}	V_{SS} 1796 ml/kg (902–2871)		
1.0 h (1.0-1.1)	26.1 µg*h/ml (12.6-41.5) AUC_{0-12}	7.7 h (4.2-14.6)	192.1 ml/h/kg (120.5–396.8) CL_{SS}	V_{SS}		
Arithmetic mean(CV%)	Geometric mean(CV%)*	NR	NR	NR	Arithmic mean(CV%)	[52]
1.36 h (15)	11.722 µg*h/ml (76)					
1.97 h (0)	21.931 µg*h/ml (125)					
1.50 h (144)	3.788 µg*h/ml (78) AUC_{tau}				NR NR 43.6 % (88)	
1.36 h (16)	11.954 µg*h/ml (78)					
1.97 h (0)	24.047 µg*h/ml (129)					
1.33 h (82)	7.346 µg*h/ml (60) AUC_{tau}				NR NR 90.0% (86)	
1.36 h (15)	11.827 µg*h/ml (75)					
1.97 h (0)	22.914 µg*h/ml (125)					
1.43 h (122)	5.184 µg*h/ml (71) AUC_{tau}				NR NR 66.0 % (97)	
Arithmic mean(CV%)	Geometric mean(CV%)*	NR	NR	NR	Arithmic mean(CV%)	
1.97 h (0)	18.216 µg*h/ml (87)					
2.63 h (0)	25.566 µg*h/ml (81)					
1.00 h (58)	6.959 µg*h/ml (104) AUC_{tau}				NR NR 63.4 % (88)	
2.17 h (30)	16.234 µg*h/ml (60)					
3.04 h (22)	34.681 µg*h/ml (81)					
1.72 h (98)	10.076 µg*h/ml (56) AUC_{tau}				NR NR 66.7% (53)	
2.07 h (22)	17.249 µg*h/ml (80)					
2.84 h (18)	29.776 µg*h/ml (82)					
1.34 h (93)	8.373 µg*h/ml (80) AUC_{tau}				NR NR 65.1 % (70)	

Table 9. Continued

Population	Dose	Formulation	Weight	N	SD, FD or MD		
						C_{max}	C_{min}
Immunocompromised haemato-oncology and non-haemato-oncology Japanese paediatric patients aged 2 to <15 years.	2 to 12 years or 12 to 15 years (<50 kg): Day 1: 9 mg/kg IV every 12h; day 2-7: 8 mg/kg IV every 12h; Day 8-14: 9 mg/kg PO every 12h (max. 350 mg). 12 to 15 years (≥50 kg); Day 1: 6 mg/kg every 12h IV; day 2-7: 4 mg/kg IV every 12h; Day 8-14: 200 mg PO every 12h.	IV and PO	Mean (range) 30.4 kg (11.5–55.2)	21	MD IV 2 to 11 years	Median(range) 8.21 µg/ml (4.62–12.6) $C_{max,ss}$	Median(range) 2.89 µg/ml (0.596–9.36) $C_{min,ss}$
					12 to 14 years (<50 kg)	7.72 µg/ml (6.24–19.6) $C_{max,ss}$	4.31 µg/ml (3.09–10.4) $C_{min,ss}$
					12 to 14 years (≥50 kg)	3.22 µg/ml (2.32–4.12) $C_{max,ss}$	0.576 µg/ml (0.471–0.680) $C_{min,ss}$
					All	7.72 µg/ml (2.32–19.6) $C_{max,ss}$	3.00 µg/ml (0.471–10.4) $C_{min,ss}$
					MD PO 2 to <12 years	Median(range) 6.70 µg/ml (3.58–18.3) $C_{max,ss}$	Median(range) 2.06 µg/ml (0.148–12.3) $C_{min,ss}$
					12 to 14 years (<50 kg)	6.21 µg/ml (6.13–13.0) $C_{max,ss}$	3.00 µg/ml (1.09–6.59) $C_{min,ss}$
					12 to 14 years (≥50 kg)	2.03 µg/ml ** $C_{max,ss}$	0.306 µg/ml ** $C_{min,ss}$
					All	6.48 µg/ml (2.03–18.3) $C_{max,ss}$	2.06 µg/ml (0.148–12.3) $C_{min,ss}$
Haemato-oncology and HSCT adolescents aged 12 to <17 years.	6 mg/kg IV every 12 h on day 1 followed by 4 mg/kg IV every 12h for the next 6 days and were switched to 300 mg PO every 12h.	IV and PO	Median(range) 57.1 kg (30.4-92.2)	26	SD/MD	Median(range)	Median(range)
					Day 1 IV	2.36 µg/ml (0.66-4.02) C_{max}	NR
					Day 7 IV	3.72 µg/ml (1.171-9.99) $C_{max,ss}$	1.59 µg/ml (0.08-7.78) $C_{min,ss}$
					Day 7 PO	2.84 µg/ml (0.18-5.88) $C_{max,ss}$	1.05 µg/ml (0.04-2.84) $C_{min,ss}$

Abbreviations: IV=intravenous; PO='per os' (oral administration); N=total patients; SD=single dose; FD=first dose; MD=multiple dose; C_{max}=maximum concentration in blood/plasma; C_{min}= minimal concentration in blood/plasma; C_{avg}=average plasma concentration; T_{max}=time to reach C_{max}; AUC=area under the curve; $T_{1/2}$=elimination half-life; CL=clearance; V_d=volume of distribution; F=bioavailability; NR=not reported; SS=steady state; (SD)=standard deviation; (IQR)=interquartile range; HSCT= Haematopoietic stem cell transplantation; BMT= bone marrow tranplantation

Pharmacokinetic parameters						Reference
T_{max}	AUC	$T_{1/2}$	CL	V_d	F	
Median(range)	Median(range)	NR	NR	NR	NR	[54]
2.96 h (0.950–4.00)	60.2 µg*h/ml (23.0–103) $AUC_{0-12,ss}$					
4.00 h (2.92–4.20)	70.5 µg*h/ml (55.7–177) $AUC_{0-12,ss}$					
1.34 h (1.00–1.67)	17.6 µg*h/ml (14.2–21.0) $AUC_{0-12,ss}$					
2.96 h (0.950–4.20)	59.3 µg*h/ml (14.2–177) $AUC_{0-12,ss}$					
Median(range)	Median(range)	NR	NR	NR	NR	
1.09 h (0.917–3.78)	45.6 µg*h/ml (12.4–156) $AUC_{0-12,ss}$					
1.00 h (0.950–2.03)	49.4 µg*h/ml (36.3–117) $AUC_{0-12,ss}$					
1.00 h**	10.0 µg*h/ml ** $AUC_{0-12,ss}$					
1.04 h (0.917–3.78)	45.6 µg*h/ml (10.0–156) $AUC_{0-12,ss}$					
Median(range)	Median(range)	NR	NR	NR	NR	[50]
1.97 h (1.90-2.08) T_{max}	9.51 µg*h/ml (2.52-21.6) AUC_{0-12}					
1.30 h (1.17-3.95) $T_{max,ss}$	27.9 µg*h/ml (6.24-95.3) $AUC_{0-12,ss}$					
2.00 h(0.67-8.10) $T_{max,ss}$	18.7 µg*h/ml (1.17-49.7) $AUC0_{0-12,ss}$					

*Values recalculated/adjusted from original paper to create uniformity of units
**Values from 1 patient

Table 10. Population pharmacokinetic estimates of voriconazole

Population	Dose	Formulation	Weight	N	SD, FD or MD	AUC	T	TI_{ag}	CL
Haemato-oncology patients and patients with other diseases aged 8-15 years	NR	IV and PO	NR	55	MD	NR	NR	NR	NR
Immunocom-promised children and adolescents aged 2-17 years (also adult data included)	2 to <12 years IV: Day 1: 6 mg/kg every 12h; Day 2-4: 3 mg/kg every 12 h; Day 5-8: 4 mg/kg every 12 h. 2 to 12 years IV and PO: Day 1: 6 mg/kg IV every 12h; Day 2-4: 4 mg/kg IV every 12 h; Day 5-8: 6 mg/kg IV every 12 h; Day 9-12: 4 mg/kg PO every 12h. Or Day 1-4: 6 mg/kg IV every 12h; Day 5-8: 8 mg/kg IV every 12 h; Day 9-12: 6 mg/kg PO every 12h. Or Day 1-7: 7 mg/kg IV every 12 h; Day 8-14 200 mg PO every 12 h. 12 to<17 years IV and PO: Day 1: 6 mg/kg IV every 12h; Day 2-7: 4 mg/kg IV every 12h; Day 8-14: 300 mg PO every 12 h. Adults: Day 1: 6 mg/kg IV every 12h; Day 2-7: 4 mg/kg IV every 12h; Day 8-14: 200 mg PO every 12 h.	IV and PO (tablet and suspension)	Median (range) Children: 20.1 kg (10.8–54.9) Adolescents: 57.1 kg (30.4–92.2) Adults: 76.0 kg (49.0-97.0)	112 children 26 adolescents 35 adults	MD	NR	Value (RSE%) T_{50} = 2.41 h (6.6)	$0.949 \cdot (1 + (-0.874 \times (1\text{-STDY5, adult}))$ #	$6.16 \times (WT/70)^{0.75}$
HSCT patients aged 2 to ≤12 years and >12 years**	≤12 years: 7 mg/kg every 12h IV >12 years: 6 mg/kg every 12h for the first 24 h, followed by 4 mg/kg every 12h thereafter. If possible switched to PO with a fixed dose of 200 mg every 12h for all age groups.	IV and PO	Value range) ≤12 years: 27 kg (7–44) >12 years: 56 kg (39–85)	23	MD	NR	NR	NR	NR

Pharmacokinetic parameters										Reference
V1	**Q1**	**V2**	**Q2**	**V3**	**K**	**F**	**V_{max}**	**$V_{max,inh}$**	**K_m**	
WtMedian (95% CI) 0.67 L/kg (0.61-0.70)	NR	NR	NR	NR	WtMedian (95% CI) 0.79 1/h (0.58-0.86) K_a Median (range) 0.49 1/h (0.04-0.94) K_{cp} Median (range) 0.091/ h (0.07-0.28) K_{pc}	WtMedian (95% CI) 0.48 (0.40-0.56)	WtMedian (95% CI) 1.24 mg/h/kg$^{0.75}$ (0.79-.180)	NR	WtMedian (95% CI) 5.3 mg/L (2.94-5.98)	[56]
79.0 × WT/70	*15.5* × (WT/70)$^{0.75}$ × (1 + 0.637 × (1 - STDY5,adult))#	103 × WT/70	NR	NR	(1.19 × (1 - 0.615· STDY4,adol) × (1 - STDY5,adult) + 0.0912 × STDY5,adult)# K_a	Value (RSE%) 0.585(13) logit(F)	114 × (WT/70)$^{0.75}$ × (1 + (- 0.382 × STDY1,ped))# $V_{max,\ 1h}$ Concentration and time-dependent Vmax.	1.50 + (–0.390 × (AGE < 12))## logit($V_{max,inh}$)	1.15 × (1 + (- 0.382 × STDY1,ped))#	[57]
Value(RSE%) 228 L/70kg (13.5)	Value(RSE%) 21.9 L/h/70kg (19.7)	Value(RSE%) 1430 L/70 Kg (22.6)	NR	NR	Value(RSE%) 1.19 1/h (-) K_a FIXED	Value(RSE%) 59.4 % (17.8)	Value (RSE%) 51.5 mg/h/70 kg (15)		Value (RSE%) 1.15 mg/L (-) FIXED	[58]

Table 10. Continued

Population	Dose	Formulation	Weight	N	SD, FD or MD	AUC	T	TI_{ag}	CL
Patients with haematological malignancies or other diseases aged 2 to <12 years	Study A SD IV: 3 and 4 mg/kg Study B/C MD IV: 3, 4, 6, and 8 mg/kg every 12h (Study B), followed by MD PO 4 and 6 mg/kg every 12h (study C).	IV and PO (suspension)	Median(range) 22.8 kg (10.8 to 54.9)	82	MD	NR	NR	NR	Value (RSE%) 0.582 L/h/kg (19) CL in EMs Decreased in CL for HEMs/PMs (35.5%)
Immuncom-promised Japanese children aged 2 to <15 years.	2 to 12 and 12 to 15 years (<50 kg): Day 1: 9 mg/kg IV every 12h; Day 2-7: 8 mg/kg IV every 12h; Day 8-14: 9 mg/kg PO every 12h (max. 350 mg) 12 to 15 years (≥ 50 kg): Day 1; 6 mg/kg every 12h IV; Day 2-7: 4 mg/kg IV every 12h; Day 8-14: 200 mg PO every 12h.	IV and PO (suspension)	Median(range) 31.5 kg (11.5–55.2)	21	MD	NR	Estimate(RSE%) 2.45 h (6.3)	Estimate(RSE%) 0.121 h (2.8) A_{lag}	CL = 6.02 × $(WT/70)^{0.75}$
Patients with haematological malignancies or other diseases aged 2 to <12 years (and healthy adults)	Children: Mean dose (range) of 5.6 mg/kg (3.0–8.4) Adults: Mean dose (range) of 2.8 mg/kg (1.8–4.4)	IV and PO	Mean(range) Children 22.7 kg (10.8–54) Adults 75.8 kg (49–97)	141 (85 children and 56 adults)	MD	NR	NR	NR	NR
Immuno-compromised with haematological and non-haematological malignancies, liver transplantation, CF, immunodeficiency or autoimmune disease and oncology patients aged 0.8–20.5 years	Median(range) IV: 150 mg (55-180), 6.0 mg/kg (3.4–10.5). PO or nasogastrically: 200 mg (30–600), 5.3 mg/kg (2.0–12.9).	IV and PO	Median(range) 33.3 kg (6.5-102.2)	40	MD <12 years ≥12 years	NR	NR	Geometric mean (GRSE%) 4.17 h (13) 4.14 h (11)	Geometric mean (GRSE%) 0.32 L/kg/h (125) 0.20 L/kg/h (170)
Immuno-compromised children aged 2 to 11 years	SD: 3 or 4 mg/kg MD; Day 1:loading dose of 6 mg/kg every 12h; Day 2-4: 3 mg/kg every 12h; Day 4-8: 4 mg/kg every 12h.	IV	Mean (range) 23.4 kg (12-54)	11(SD) 28(MD)	MD	NR	median (5th and 95th percentiles) 7.5h (3.5- 21.4) $T_{1/2}$	NR	Value(RSE%)### 0.40 L/h/kg (14) CL in EMs Decreased CL in HEMs/PMs of 46%.

Pharmacokinetic parameters										Reference
V1	**Q1**	**V2**	**Q2**	**V3**	**K**	**F**	**V_{max}**	**$V_{max,inh}$**	**K_m**	
Value (RSE%) 0.807 L/kg (14)	Value (RSE%) 0.609 L/h/kg (13)	Value(RSE%) 2.17 L/kg (11)	NR	NR	Value(RSE%) 0.849 1/h (40) K_a	Value (RSE%) 44.6 % (14)	NR		Value(RSE%)* 3.030 mg/L (45)	[62]
75.0 × (WT/70)	24.6 × (WT/70)$^{0.75}$	101 × (WT/70)	NR	NR	Estimate (RSE%) 1.38 1/h (14) k_a	Estimate(RSE%) 0.597 (13) logit(F)	118 × (WT/70)$^{0.75}$ $V_{max,\ 1h}$ Concentration and time-dependent Vmax.	Estimate(RSE%) 2.61 (19) logit($V_{max,inh}$)	Estimate (RSE%)* 0.922 mg/L (30)	[59]**
WtMedian (95% CI) 1.20 L/kg (1.09–1.31) $V_{central}$	NR	NR	NR	NR	WtMedian (95% CI) 1.53 1/h (1.14–1.78) K_a 0.40 1/h (0.37–0.43) K_{cp} 0.15 1/h (0.12–0.17) K_{pc}	WtMedian (95% CI) 0.85 (0.77–0.89)	WtMedian (95% CI) 1.82 mg/h/kg$^{0.75}$ (0.52–3.09)		WtMedian (95% CI) 1.54 mg/L (1.06–1.72)	[60]
Geometric mean (GRSE%) 0.27 L/kg (188) 0.17 L/kg (188)	Geometric Mean (GRSE%) 0.43 L/kg/h (246) 0.68 L/kg/h (191)	Geometric mean (GRSE%) 2.34 L/kg (42) 0.83 L/kg (127)	NR	NR	Geometric Mean (GRSE%) 0.51 1/h (164) K_a 0.43 1/h (212) K_a	Geometric mean (GRSE%) 75% (35) 81% (37)	NR		Geometric mean (GRSE%) 5.16 mg/L (9) 7.84 mg/L (5)	[55]
Value (RSE%)### 0.80 L/kg (20)	Value (RSE%)### 0.64 L/h/kg (15)	Value (RSE%)### 1.7 L/kg (7.5%)	NR	NR	NR	NR	NR		NR	[61]

Table 10. Continued

Population	Dose	Formulation	Weight	N	SD, FD or MD	AUC	T	TI_{ag}	CL
Patients undergoing HSCT aged <2-21 years		IV	NR	59	MD	NR	NR	NR	4.60 × (WT/70)$^{0.75}$ × [(Age$^{Hill\ coef}$)/ (Age$^{Hill\ coef}$ + TM$^{Hill\ coef}$)] $CL_{voriconazole}$ 3.62 × (WT/70)$^{0.75}$ Apparent $CL_{metabolite}$

Abbreviations: N=total patients; SD=single dose; FD=first dose; MD=multiple dose; AUC=area under the curve; T_{lag}= lagtime; T_{50} = time at half of the maximum inhibition of V_{max}; $T_{1/2}$=elimination half-life; CL=clearance; V1= volume of distribution of the central compartment; Q1=intercompartmental clearance; V2= volume of distribution of the peripheral compartment; Q2 = intercompartmental clearance; V3= volume of distribution of the peripheral compartment; K_a = rate of oral bioavailability; K_{cp} = rate constant from central to peripheral compartment; K_{pc} = rate constant from peripheral to central compartment; F=bioavailability; V_{max}= maximum rate of enzyme activity; $V_{max,\ inh}$ = maximum fraction of the V_{max} inhibition; K_m= Michaelis-Menten constant; PO='per os'; IV=intravenous; NR=not reported; WtMedian= weighted median; CI= confidence interval; RSE=relative standard error; GRSE= geometric relative standard error; HSCT= Haematopoietic stem cell transplantation; CF=cystic fibrosis; EMs=homozygous extensive CYP2C19 metabolizers, HEMs= heterozygous extensive CYP2C19 metabolizes; PMs=poor CYP2C19 metabolizers; Hill coef= hill coefficient fixed to 1.

Pharmacokinetic parameters										Reference
V1	Q1	V2	Q2	V3	K	F	V_{max}	$V_{max,inh}$	K_m	
52.4 × (WT/70)[1]	13.3 × (WT/70)[0.75]	86.7 × (WT/70)[1]	NR	NR	NR	NR	36.2 × (WT/70)[0.75]	NR	Estimate(RSE%) 1.57 (34.8)	[63]

*Values recalculated/adjusted from original paper to create uniformity of units.
**Based on priors.
#Values for STDY1,ped; STDY4,adol and STDY5,adult indicate variables of 0 or 1, dependent on the study group.
##$V_{max, inh}$ =100% if CYP2C19 is equal to HEM or PM.
###Estimates for a typical model patient, but the typical model patient is not defined.

Table 11. Pharmacokinetic models of voriconazole

Population	Subjects N	Samples N	Program	Covariates tested	Compartments	PO/IV	
							CL
Children and adolescent cancer patients aged 8-15	55	158	Pmetrics	Ethnic group, age, sex, WT, hepatic dysfunction	2, with first-order absorption and nonlinear elimination	PO and IV	NR
Immunocompromised children and adolescents aged 2-17 years.	112 children 26 adolescents 35 adults	2022 554 760	NONMEM	Age, WT, CYP2C19 genotyping status, and formulation type (POS/tablet)	2, with first order absorption and mixed linear and nonlinear elimination	PO and IV	Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg
Immunocompromised children aged 2 to ≤12 years and > 12 years.	23	187	NONMEM	Age, sex, WT, CRP, bilirubin, AST, ALT, GGT, AP, creatinine.	2, with first order absorption and nonlinear elimination	PO and IV	NR
Immunocompromised children aged 2 to <12 years.	82	1274	NONMEM	Age, gender, WT, HT, ethnic origin, serum creatinine, AST, ALT , AP, GGT, ALB, , total bilirubin, total protein levels, CYP2C19, CYP2C9 and CYP3A4 inhibitors, CYP450 inducers, leukaemia, BMT, aplastic anemia, lymphoma, or other, CYP2C19 genotype status and presence of mucositis.	2, with first order absorption and nonlinear elimination	PO and IV	WT, CYP2C19 genotype, ALT(loglinear)
Immunocompromised Japanese children aged 2 to <15 years	21	276	NONMEM	WT, age, gender, CYP2C19 genotyping status, liver function parameters	2, with first order absorption and mixed linear and nonlinear elimination	PO and IV	Allometrically scaled WT with a fixed exponent of 0.75 and normalised to 70 kg
Patients with haematological malignancies or other diseases aged 2 to <12 years (and healthy adults)	141	Mean (STDV) Children 20.3(5.4) Adults 36.5(22.1)	Pmetrics	WT, age, allometric scaling	2, with first order absorption and nonlinear elimination	PO and IV	NR
Immunocompromised children aged 0.8–20.5 yrs	40	108	NPAG	WT, age, sex, creatinine clearance, ALT, AP	2, with delayed absorption and nonlinear elimination	PO and IV	WT, age
immunocompromised children aged 2 to 11 years	35	355	NONMEM	WT, CYP2C19 genotype, ALT, AP	2, with linear elimination	IV	WT, CYP2C19 genotype, ALT (loglinear) and AP (loglinear)

Covariates in final model									Reference
V1	**Q1**	**V2**	**Q2**	**V3**	**K**	**V_{max}**	**$V_{max,inh}$**	**F**	
NR	NR	NR	NR	NR	NR	Allometrically scaled bodyweight with a fixed exponent of 0.75	NR	NR	[56]
Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg	Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg	Allometrially scaled WT with a fixed exponent of 1 and normalized to 70 kg	NR	NR	NR	Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg	CYP2C19 genotyping status was only included in adult patients	NR	[57]
Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg	Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg	Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg	NR	NR	NR	Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg	NR	NR	[58]
WT	WT	WT	NR	NR	NR	NR	NR	NR	[62]
Allometrically scaled WT with a fixed exponent of 1 and normalised to 70 kg	Allometrically scaled WT with a fixed exponent of 0.75 and normalised to 70 kg	Allometrically scaled WT with a fixed exponent of 1 and normalised to 70 kg	NR	NR	NR	Allometrically scaled WT with a fixed exponent of 0.75 and normalised to 70 kg	NR	NR	[59]
Allometrically scaled WT with a fixed exponent of 1	NR	NR	NR	NR	NR	Allometrically scaled WT with a fixed exponent of 0.75	NR	NR	[60]
WT, age	WT	WT, age	NR	NR	NR	NR	NR	NR	[55]
WT	WT	WT	NR	NR	NR	NR	NR	NR	[61]

Table 11. Continued

Population	Subjects N	Samples N	Program	Covariates tested	Compartments	PO/IV	CL
Patients undergoing HSCT aged <2-21 years	59	1288	NONMEM	WT, maturation function for voriconazole	2-compartments for voriconazole and 1-compartment for its metabolite, with linear voriconazole elimination but also nonlinear voriconazole elimination to its metabolite.		Allometrically scaled bodyweight with a fixed exponent of 0.75 and normalised to 70 kg for both voriconazole and metabolite; maturation factor for voriconazole

Abbreviations: N=total patients or samples; NPAG= non-parametric adaptive grid modeling; NONMEM= nonlinear mixed effect modeling; SD=single dose; MD=multiple dose; PO='per os'; IV=intravenous; CL=clearance; V1= volume of distribution of the central compartment; Q1=intercompartmental clearance; V2= volume of distribution of the peripheral compartment; Q2 = intercompartmental clearance; V3= volume of distribution of the peripheral compartment; K = rate constant; F=bioavailability; V_{max}= maximum rate of enzyme activity; NR=not reported; HSCT= Haematopoietic stem cell transplantation;

Covariates in final model									Reference
V1	**Q1**	**V2**	**Q2**	**V3**	**K**	**V_{max}**	**$V_{max,inh}$**	**F**	
Allometrically scaled bodyweight with a fixed exponent of 1 and normalised to 70 kg	Allometrically scaled bodyweight with a fixed exponent of 0.75 and normalised to 70 kg	Allometrically scaled bodyweight with a fixed exponent of 1 and normalised to 70 kg	NR	NR	NR	Allometrically scaled bodyweight with a fixed exponent of 0.75 and normalised to 70 kg	NR	NR	[63]

CF=cystic fibrosis; WT=weight; HT=height; POS=powder for oral suspension; CRP= C-reactive protein; AST= aspartate aminotransferase; ALT= Alanine aminotransferase; GGT= gamma-glutamyl transferase; AP= alkaline phosphatase; ALB=albumin.

Table 12. Non-compartmental analyses of posaconazole

Population	Dose	Formulation	Weight	N	SD, FD or MD	Pharmacokinetic parameters
						C_{max}
Paediatric patients with haematological, non-haematological malignancies or HSCT and neutropenia aged 3 months to <18 years.	7 to <18 years; 6 mg/kg PO every 12h or 9 mg/kg PO every 12h or 6 mg/kg every 8h PO for 7-28 days.	PO (suspension)	Median 29.8 kg	136	Day 1 FD 3 mo to <2 years 6 mg/kg BID PO	Value[#] 103 ng/ml[**]
	2 to <7 years; 6 mg/kg every 12h PO or 9 mg/kg every 12h PO or 6 mg/kg every 12h PO for 7-28 days.				2 to <7 years 6 mg/kg (BID PO) 9 mg/kg (BID PO) 6 mg/kg (TID PO)	 196 ng/ml (93.9) 175 ng/ml (70.5) 109 ng/ml (61.3)
	3 months to <2 years 6 mg/kg every 12h PO or via enteral tube for 7-28 days.				7 to <18 years 6 mg/kg (BID PO) 9 mg/kg (BID PO) 6 mg/kg (TID PO)	 156 ng/ml (78.1) 162 ng/ml (86.7) 93.2 ng/ml (60.8)
					Day 7 MD 3 mo to <2 years 6 mg/kg BID PO	Value[#] 520 ng/ml**
					2 to <7 years 6 mg/kg BID PO 9 mg/kg BID PO 6 mg/kg TID PO	 726 ng/ml (125.5) 581 ng/ml (61.0) 705 ng/ml (60.9)
					7 to <18 years 6 mg/kg BID PO 9 mg/kg BID PO 6 mg/kg TID PO	 1200 ng/ml (75.5) 1390 ng/ml (111.4) 1230 ng/ml (64.2)
Children with a haematological malignancies aged 2–13 years	120 mg/m^2 every 8h	PO (suspension)	Mean (STDV) 19.9 kg (6.1)	14	MD	Mean (STDV)* 960 ng/ml (630)
Haematology and oncology patients with documented or expected neutropenia aged 2-17 years	3.5, 4.5 or 6.0 mg/kg IV every 12 hours on day 1, followed by 3.5, 4.5 or 6.0 mg/kg (max 300 mg) once daily at day 2 to 10 and were switched to PFS in the same daily dose.	PO (IV or powder for oral suspension)	NR	118	2-6 years MD 3.5 mg/kg (IV) 4.5 mg/kg (IV) 6.0 mg/kg (IV)	Geometric mean (%GCV) 1590 ng/ml (43.1) 2320 ng/ml (39.8) 3060 ng/ml (54.1)
					3.5 mg/kg (PFS) 4.5 mg/kg (PFS) 6.0 mg/kg (PFS)	884 ng/ml (44.4) 1550 ng/ml (40.8) 1510 ng/ml (43.4)
					7-17 years MD 3.5 mg/kg (IV) 4.5 mg/kg (IV) 6.0 mg/kg (IV)	Geometric mean (%GCV) 2450 ng/ml (72.7) 2310 ng/ml (40.3) 3340 ng/ml (39.4)
					3.5 mg/kg (PFS) 4.5 mg/kg (PFS) 6.0 mg/kg (PFS)	1340 ng/ml (30.8) 1670 ng/ml (28.5) 1370 ng/ml (178.5)

							Reference
C	**T_{max}**	**AUC**	**$T_{1/2}$**	**CL**	**V_d**	**F**	
Arithmetic mean (%CV,STDV)	Median(min-max)	Value#	NR	NR	NR	NR	[74]
68.5 ng/ml**	3.38 h**	574 ng*h/ml AUC_{0-12}**					
		AUC_{tf}					
122 ng/ml (83.1, 101)	5.01 h (2.92, 11.60)	1300 ng*h/ml (91.4) AUC_{0-12}					
112 ng/ml (77.6, 86.9)	3.99 h (2.98, 11.08)	1210 ng*h/ml (76.88) AUC_{0-12}					
68.4 ng/ml (59.2, 40.4)	7.95 h (2.98, 8.00)	544 ng*h/ml (59.6) AUC_{0-8}					
C_{avg}		AUC_{tf}					
107 ng/ml (86.5, 92.5)	5.0 h (2.97, 12.0)	1140 ng*h/ml (93.7) AUC_{0-12}					
113 ng/ml (89.1, 100)	3.12 h (2.92, 8.00)	1270 ng*h/ml (98.1) AUC_{0-12}					
57.9 ng/ml (52.2, 30.2)	4.88 h (2.92, 8.08)	424 ng*h/ml (49.5) AUC_{0-8}					
C_{avg}		AUC_{tf}					
Arithmetic mean (%CV,STDV)	Median(min-max)	Value#	NR	NR	NR	NR	
453 ng/ml**	0.00 h**	3590 ng*h/ml AUC_{0-12}**					
Cavg		AUC_{tf}					
604 ng/ml (129.0,779)	4.13 h (0.0, 11.17)	6770 ng*h/ml (138.9) AUC_{0-12}					
485 ng/ml (63.0,306)	3.00 h (0.0, 8.08)	5350 ng*h/ml (62.0) AUC_{0-12}					
620 ng/ml (66.2, 411)	3.00 h (0.0, 5.08)	4920 ng*h/ml (67.1) AUC_{0-8}					
C_{avg}		AUC_{tf}					
1050 ng/ml (76.2, 789)	4.58 h (0, 7.75)	11800 ng*h/ml (75.4) AUC_{0-12}					
1240 ng/ml (113.4, 1400)	4.03 h (0.0, 28.5)	13500 ng*h/ml (115.8) AUC_{0-12}					
1150 ng/ml (65.4, 750)	2.63 h (0.00, 7.62)	8310 ng*h/ml (74.9) AUC_{0-8}					
C_{avg}		AUC_{tf}					
Mean (STDV)*	NR	Mean (STDV)*	NR	Median (IQR)*	NR	NR	[75]
860 ng/ml (580)		20500 ng*h/ml (14000)		15.9 L/h (9.95-27.86)			
C_{avg}		AUC_{0-24}		CL/F			
Geometric mean (%GCV)	Median(min–max)	Geometric mean (%GCV)	NR	Geometric mean (%GCV)	NR	NR	[76]
743 (55.0)	1.78 h (1.67-5.53)	17800 ng*h/ml (55.0)		3.39 L/h (52.8)			
1070 (30.0)	1.78 h (1.42-5.90)	25600 ng*h/ml (30.0)		2.97 L/h (36.2)			
1300 (48.9)	1.75 h (1.57-1.83)	31100 ng*h/ml (48.9)		3.27 L/h (49.3)			
C_{avg}		AUC_{0-24}		CL			
510 (36.0)	3.83 h (1.92-4.25)	12200 ng*h/ml (36.0)		4.97 L/h (29.1)			
901 (64.5)	3.82 h (1.88-5.92)	21600 ng*h/ml (64.5)		3.49 L/h (59.1)			
960 (47.3)	4.00 h (2.17-7.92)	23000 ng*h/ml (47.3)		4.60 L/h (35.2)			
C_{avg}		AUC_{0-24}		CL/F			
Geometric mean (%GCV)	Median(min–max)	Geometric mean (%GCV)	NR	Geometric mean (%GCV)	NR	NR	
1140 ng/ml (49.7)	1.77 h (0-3.5)	27300 ng*h/ml (49.7)		6.64 L/h (38.6)			
1240 ng/ml (42.9)	1.75 h (1.52-1.80)	29800 ng*h/ml (42.9)		6.69 L/h (37.3)			
1930 ng/ml (41.5)	1.77 h (1.33-6.00)	44200 ng*h/ml (41.5)		4.76 L/h (55.7)			
C_{avg}		AUC_{0-24}		CL			
861 ng/ml (33.8)	2.20 h (1.92-6.03)	20700 ng*h/ml (33.8)		7.67 L/h (39.9)			
1200 ng/ml (33.7)	6.14 h (1.98-7.98)	28700 ng*h/ml (33.7)		7.84 L/h (49.4)			
1040 ng/ml (184.3)	2.78 h (0-4.00)	25000 ng*h/ml (184.3)		8.39 L/h (190.3)			
C_{avg}		AUC_{0-24}		CL/F			

Table 12. Continued

Abbreviations: IV=intravenous; PO='per os' (oral administration); N=total patients; SD=single dose; FD= first dose; MD=multiple dose; C_{max}=maximum serum concentration in blood; Cavg=average serum concentration; T_{max}=time to reach C_{max}; AUC=area under the curve; AUC_{tf} = AUC from 0 to final quantifiable sample; $T_{1/2}$=elimination half-life; CL=clearance; V_d=volume of distribution; F=bioavailability; PFS=powder for suspension; BID=twice daily; TID=three times daily; NR=not reported; SS=steady state; STDV=standard deviation; IQR=interquartile range; HSCT= Haematopoietic stem cell transplantation; STDV=standard deviation; CV= Coefficient of variation; GCV= geometric coefficient of variation; IQR=interquartile range.

*Values recalculated/adjusted from original paper to create uniformity of units
**Values from one patient
#Unclear whether mean or median values are reported. Type of error was not mentioned.

Table 13. Population pharmacokinetic estimates of posaconazole

Population	Dose	Formulation	Weight	N	SD, FD or MD		
						AUC	$T_{1/2}$
Immunocompromised children aged 5 months to 18 years	Dose (range) 13.11 mg/kg (2.67–48.95)	PO (tablet and suspension)	Weight (range) 17.8 kg (6.05–74.8)	117	MD	NR	NR

Abbreviations: N=total patients; SD=single dose; FD= first dose; MD=multiple dose; AUC=area under the curve; $T_{1/2}$=elimination half-life; CL=clearance; V_d=volume of distribution; K_a= rate of oral bioavailability; F=bioavailability; f_D= fractional decrease of the bioavailability in patients with diarrhea (suspension); f_p= fractional decrease of the bioavailability in patients using proton pump inhibitors (suspension); PO='per os';

Pharmacokinetic parameters						Reference
CL	**V1**	**K_a**	**F**	**f_D**	**f_P**	
$14.95 \times (WT/70)^{0.75}$ CL/F	$201.7 \times (WT/70)^{1}$ V/F	Estimate(%RSE) 0.197 1/h (fixed) K_a, suspension 0.588 1/h (fixed) K_a, tablet	NR	Estimate(%RSE) -0.33 (28)	Estimate(%RSE) -0.42 (14)	[77]

NR=not reported; CL/F= apparent clearance; V/F=apparent volume of distribution; RSE=relative standard error.

Table 14. Pharmacokinetic models of posaconazole

Population	Subjects N	Samples N	Programme	Covariates tested
Immunocompromised children aged 5 months to 18 years	117	338	NONMEM	Diarrhoea, treatment/prophylaxis, macrolides, echinocandins, terbinafine, ciclosporin, tacrolimus, mycophenolate, rifamycins, carbamazepine, phenytoin, histamine H2-receptor antagonists, proton pump inhibitors (PPIs) or valaciclovir on bioavailability Macrolides, echinocandins, ciclosporin, tacrolimus, mycophenolate, rifampicin, carbamazepine, phenytoin or valaciclovir on clearance. WT, sigmoidal maturation function based on PMA.

Abbreviations: N=total; PO=’per os’; IV=intravenously; CL=clearance; V=volume of distribution; K_a= rate of oral bioavailability; F=bioavailability. PMA = postmenstrual age.

Compartments	PO/IV	Covariates in final model				Reference
		CL	V	K_a	F	
1	PO	Allometrically scaled WT with a fixed exponent of 0.75 and normalised to 70 kg.	Allometrically scaled WT with a fixed exponent of 1 and normalised to 70 kg.	NR	Diarrhea, concurrent PPI administration	[77]

Author contribution statement

DB performed the literature search, selected articles drafted the manuscript together with RB. WT, TW and EM provided critical revision of the manuscript. All authors provided approval of the final version.

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CHAPTER 4

PHARMACOKINETIC INVESTIGATIONS OF ISAVUCONAZOLE IN PAEDIATRIC CANCER PATIENTS SHOW REDUCED EXPOSURE OF ISAVUCONAZOLE AFTER OPENING CAPSULES FOR ADMINISTRATION VIA A NASOGASTRIC TUBE

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Abstract

Objectives

To study the isavuconazole pharmacokinetics in a real-life paediatric cohort and confirming whether the isavuconazole exposures are within the adult exposure range. Furthermore, we are the first to describe unbound isavuconazole pharmacokinetics.

Methods

In this prospective, observational study, the isavuconazole dosing regimen was as follows (intravenous/oral/nasogastric tube): 5.4 mg/kg isavuconazole (maximum 200 mg/dose) three times daily on days 1-2, followed by 5.4 mg/kg isavuconazole (maximum 200 mg/dose) once daily. At least one pharmacokinetic curve was assessed. Nonlinear mixed effects modelling was used for analysis. Monte Carlo simulations were performed with the abovementioned maintenance dose for intravenous administrations and a weight band dosing regimen for oral/nasogastric tube administrations: I) <18 kg (100 mg daily); II) 18-37 kg (150 mg daily); III) >37 kg; 200 mg daily.

Results

Seventeen paediatric patients with a median age and weight of 9 years (range 1-17) and 26.0 kg (range 8.4-78.5), respectively, were evaluated. A two-compartment model describing linear pharmacokinetics of the unbound concentrations and saturable protein binding fitted the isavuconazole concentrations best. The absolute bioavailability of isavuconazole was 41.0% (95% CI: 32.4%-50.8%). The median (IQR) simulated exposures ($AUC_{0-24h,SS}$) of the total isavuconazole concentrations after intravenous and oral/nasogastric tube administration were 87.7 mg·h/L (70.5-105.1) and 50.3 mg·h/L (39.0-62.4), respectively. The unbound isavuconazole fraction (unbound/total) ranged from 0.5%-2.3%.

Conclusions

This study revealed low bioavailability after nasogastric tube administration with opened capsules. Isavuconazole exposures were in the expected range following intravenous administration. Total and unbound isavuconazole pharmacokinetics were reported with a five-fold range in the unbound fraction.

Introduction

Paediatric patients with invasive fungal disease (IFD) are treated with triazole drugs as first-line agents.[1] Posaconazole and voriconazole have shown adverse effects and many drug-drug interactions are present.[2] Isavuconazole has shown a broad antifungal spectrum, predictable pharmacokinetics, a more favorable toxicity profile, and less abundant drug-drug interactions compared to the other drugs in the current available phase 1 and 3 studies.[3, 4] Isavuconazole has regularly been used as off-label treatment in paediatric patients but there is limited pharmacokinetic knowledge in this population.[5, 6] Recently, a paediatric dosing regimen has been proposed with a loading dose of 5.4 mg/kg isavuconazole three times daily on days 1 and 2, followed by a maintenance dose of 5.4 mg/kg isavuconazole once daily.[7] Here, we evaluated the pharmacokinetic parameters of isavuconazole in a real-life paediatric cancer cohort. Additionally, we are the first to describe unbound isavuconazole pharmacokinetics.[2]

Methods

Study design and patients

This was a prospective, observational study from November 2019 until December 2020 in paediatric cancer patients aged ≥1 years. Patients who received isavuconazole (intravenously, orally via a capsule, or enterally opened capsules via a nasogastric tube) were evaluated after informed consent. Choices for route of administration were at the discretion of the treating physician. The procedures for administration via a nasogastric tube were as follows: the capsules were opened and the content was dissolved and added in a syringe which was subsequently administered via the nasogastric tube. The dosing regimen was as follows: 5.4 mg/kg isavuconazole (maximum 200 mg/dose) three times daily on day 1 and 2, followed by 5.4 mg/kg isavuconazole (maximum 200 mg/dose) once daily.[7] At least one pharmacokinetic curve was drawn at t=0h, 1h, 2-4h, 4-6h, and 12-18h to assess the AUC. Total and unbound isavuconazole concentrations were measured with validated bioanalytical methods (Supplementary file).

Ethics

All patients signed a general informed consent for participation in scientific research in the Princess Máxima Center, Utrecht, The Netherlands. For the isavuconazole study, we received approval from the Medical Ethics Committee of Utrecht (21-342/C).

Pharmacokinetic analysis

The pharmacokinetic analysis of isavuconazole was performed using nonlinear mixed effects modelling (NONMEM), with the software package NONMEM V7.5 (Icon, Dublin, Ireland). Total and unbound isavuconazole concentrations were described integrally using a saturable protein binding model. Model development was based on physiological plausibility, statistical significance, and goodness-of-fit in line with best practice. The details of the analysis and model evaluation are described in the supplementary material, Table S1, Figures S1-S5.

The final pharmacokinetic model was used to evaluate the isavuconazole exposure after oral and intravenous dosing regimens by means of Monte Carlo simulations. Total isavuconazole concentrations were the main outcome parameter. For intravenous administrations, simulations were performed with the maintenance dose of 5.4 mg/kg/dose except for those children with a bodyweight of ≥37 kg who received a fixed dose of 200 mg. For oral and nasogastric tube administrations, a weight band dosing regimen was evaluated. The three oral dosing regimens were chosen as follows: I) <18 kg; maintenance dose of 100 mg once daily, II) 18 to 37 kg; alternating maintenance dose of 100-200 mg once daily (simulated as 150 mg once daily); and III) >37 kg; maintenance dose of 200 mg once daily.

For the simulations we used a dataset with demographic data (and their distribution) of a paediatric haematology cohort (n=590) of the Dutch Childhood Oncology Group (DCOG) We compared the paediatric exposure range with the exposure range in adults (AUC at steady state (AUC_{ss})) of 60-233 mg·h/L.[7-9]

Results

A total of 17 paediatric patients with a median age and weight of 9 years (range 1-17 years) and 26.0 kg (range 8.4-78.5 kg), respectively, were evaluable. The isavuconazole treatment duration ranged from 11 to 546 days. An overview of the indication specifics is given in the supplementary file (Table S2).

A total of 119 total and 43 unbound isavuconazole concentrations were available for analysis in 26 sampling occasions. The route of administration at these sampling occasions was intravenous (n=17), oral via a capsule (n=1), and enteral via a nasogastric tube (n=8).

The measured unbound isavuconazole concentrations ranged from 0.01-0.2 mg/L and the total isavuconazole concentrations ranged from 1.08-11.6 mg/L. The unbound

isavuconazole fraction varied almost fivefold ranging from 0.5%-2.3% (Figure S2) and the unbound fraction increased with increasing unbound concentrations.

Population Pharmacokinetic analysis

A two-compartment linear pharmacokinetic model with a saturable protein model binding described the isavuconazole concentrations best (Figure S1; supplementary file (S1)).

The absolute bioavailability (F) with 95% CI of isavuconazole was estimated to be 41.0% (32.4%-50.8%). The unbound CL (CL_u) was 337 L/h (CI: 281-413 L/h). One patient received interacting co-medication (phenobarbital), which was found to increase CL_u by 2.42 (CI: 1.36-4.12) times.

The median (IQR) simulated $AUC_{0-24h,SS}$ of the total isavuconazole concentrations after intravenous and oral/nasogastric tube administration were 87.7 mg·h/L (70.5-105.1) and 50.3 mg·h/L (39.0-62.4), respectively. The predicted isavuconazole exposures after intravenous and enteral routes of administration are depicted in Figure 1. The adult exposure range ($AUC_{0-24h,SS}$ 60-233 mg*h/L) was reached in 90% of the simulated patients after intravenous administration and in 29% of the simulated patients after enteral administration.

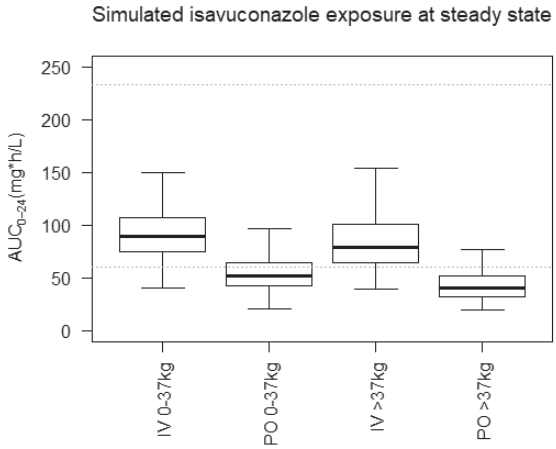

Figure 1. Predicted isavuconazole exposure after intravenous and oral administration.
The dashed lines indicate the lower (AUCss of 60 mg·h/L) and upper bound (AUCss of 233 mg·h/L) of the exposure in adult patients.

Discussion

Our most important finding is the observed low isavuconazole exposure following enteral administration of the recommended isavuconazole regimen in our paediatric cohort when compared to a recent phase I paediatric study.[7]

We found an absolute isavuconazole bioavailability of 41.0% which contradicts the bioavailability of 95% and 98% reported in immunocompromised paediatric patients and healthy adults, respectively.[2, 7] To explain this difference, we attempted to identify sources of variability within our population. The majority of our patients on enteral therapy received isavuconazole capsules over the nasogastric tube. Previously, adequate exposure has been reported after giving the intravenous solution over the naso-gastric tube in healthy adult participants.[10] At the start of our study this information was not known. Therefore, the capsules were opened and the dissolved content was administered via a tube. The handling of the capsules may have caused a loss of content. Furthermore, the drug is, according to the Stabilis database (https://www.stabilis.org/), stable for 1 h at room temperature. The hygroscopic nature of isavuconazium sulfate causes instability of the pro-drug and may have caused additional loss of content. However, in literature, comparable trough concentrations were reported after intravenous administration versus oral tube administration with opened capsules in 19 adult patients.[11] The potential impact of lower oral bioavailability might have been blurred in that study where 13 out of 19 patients received isavuconazole intravenously prior to the switch to oral treatment over a tube. Given the long terminal half-life of isavuconazole, it might take several days to weeks before the low exposure after tube administration becomes apparent.

We hypothesize that the administration of opened capsules and subsequently dissolved content over the nasogastric tube might be responsible for the low exposure after oral administration in our study. As our study was not designed to elucidate the root cause for low bioavailability, other factors, like age-dependent oral absorption, may not be ruled out. This has previously been seen in a cohort of paediatric patients receiving voriconazole: the authors hypothesized that changes in intestinal first-pass metabolism might explain the difference in bioavailability between paediatric patients and adults irrespective of oral formulation.[12] Currently, reports do not point towards such a mechanism resulting in reduced oral bioavailability in a cohort of paediatric patients.[7]

We acknowledge that our study consisted of a relatively small sample size. The obtained real-world pharmacokinetic data consequently leaded the inclusion of a wide range of age, weight and treatment duration. Therefore, our findings should be carefully interpreted.

Furthermore, our sampling strategy, contrary to the phase I paediatric report, lacks intensive sampling during the absorption phase.[7] Although a more intensive sampling strategy would have given more information on the absorption rate, it would not likely have altered our findings on the bioavailability of isavuconazole. Lastly, just one patients received isavuconazole orally versus eight patients receiving isavuconazole over the nasogastric tube. As a result, a comparison with orally administered capsules could not be made. The impact of administration of opened capsules and subsequently dissolved content over the nasogastric tube should be confirmed in a larger cohort of patients. Until then, we recommend using the reconstituted injection formulation for nasogastric tube administration, combined with therapeutic drug monitoring.[10] The intravenous fluid contains sulphuric acid and is stable for 6 hours at room temperature. Stability issues as observed for the oral formulation may thus be less pronounced.

The main goal of our study was to investigate pharmacokinetics of isavuconazole in paediatric cancer patients. We predicted that in 90% of the paediatric patients the (total) isavuconazole exposure reached the exposure in adults on a population level after intravenous administration. Although these findings cannot be directly compared to the phase I paediatric study, this predicted exposure is in the same order of magnitude as reported by the manufacturer (>80%).[7]

We also reported on total and unbound isavuconazole concentrations. Our analysis of unbound (active) isavuconazole concentrations reveals a five-fold total range in the unbound isavuconazole fraction (Figure S2), which is much larger than the reported range in the EMA assessment report.[2] When the fraction of unbound concentration varies widely, total concentrations may not correctly reflect the pharmacologically active fraction of isavuconazole. Hence, we recommend future research to focus on unbound isavuconazole concentrations.

In conclusion, isavuconazole enteral bioavailability was reduced in paediatric cancer patients. Clinicians should be aware of lower isavuconazole exposures after administration over a nasogastric tube. Administration of the reconstituted injection formulation over the nasogastric tube could be considered in combination with therapeutic drug monitoring. Furthermore, we propose utilizing unbound drug concentrations for therapeutic drug monitoring and defining target concentrations associated with efficacy and toxicity.

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Author contribution statement

Design of the protocol: DB, TW, WT, and RB. Data collection: DB. Interpretation of the data: DB, WT, RH, WT and RB. Formal statistical analysis: DB, RH, RB. Writing original draft: DB, TW, RH, WT and RB. Critical revision draft: EM, KE. Editing draft: DB, TW, RH, WT and RB. All authors provided approval of the final version.

Transparency declarations

No conflicts of interest/competing interests are applicable for this work.
Disclosures outside of this work: R.J.B. has served as a consultant to Astellas Pharma, Inc., F2G, Amplyx, Gilead Sciences, Merck Sharp & Dohme Corp., Mundipharma, and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharp & Dohme Corp., and Pfizer, Inc. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. None of the other authors have a conflict to declare.

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Supplementary data

Bioanalytical methods for total and unbound isavuconazole concentrations

Ultrafiltration of plasma at 37ºC (1,650 g for 20 minutes) with an Amicon® 30K Ultra Centrifugal filter was used to determine the unbound isavuconazole fraction. Total and unbound isavuconazole plasma concentrations were measured with a Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS) method. For total isavuconazole concentrations, this method was validated over a range of 0.05-10.0 mg/L, with an accuracy range of 95.20-100.22%, an interday precision of 0.00-2.44% and an intraday precision of 1.35-3.04% . For unbound concentrations, the validated range was 0.001-0.5 mg/L, with an accuracy range of 97.80-101.50%, an interday precision of 7.06-12.41% and an intraday precision of 3.73-8.29%.

Description of the final model

The pharmacokinetics of isavuconazole were analysed using nonlinear mixed effects modelling (NONMEM), with the software package NONMEM V7. The first-order conditional estimation with interaction (FOCE-I) method was used for model building. Inter-individual variability was assumed to be log-normally distributed and the residual variability was described by a proportional error model. Parameter uncertainty was assessed with Sampling Importance Resampling (SIR).(2). A two-compartment model fitted on total concentrations, with first-order absorption and linear elimination was used as a starting point for model building. Oral and intravenous data were fitted simultaneously. Clearance and volume of distribution were *a priori* allometrically scaled with fixed exponents of 0.75 and 1, respectively, to a total body weight of 70 kg.(2) Replacing the first-order absorption model by a zero-order absorption model did not significantly improve the model. Furthermore, adding administration via a tube as binary covariate did not significantly improve the fit of the model.

Next, total and unbound isavuconazole concentrations and fractions were visually inspected. The results are depicted in Figure S2. A clear positive relationship between unbound concentration and unbound fraction was observed, indicating saturable protein binding.(3) For total and unbound isavuconazole concentrations, a two-compartment model was developed with first order absorption, a saturable protein binding model was implemented, as described previously(4), where the protein binding constant (K_D) and maximum binding capacity (B_{max}) were estimated. Flow and volume parameters were parameterized to unbound concentrations. Albumin was not considered a significant covariate. One patient received interacting co-medication (phenobarbital), which was added as a binary covariate on unbound clearance (Cl_u) and significantly improved

the fit of the model. Interindividual variability (IIV) was estimated for Cl_u and maximum binding capacity in the protein binding model (B_{max}). A schematic overview of the model is depicted in Figure S1. Typical parameter values for the final isavuconazole model are summarized in Table S2. Goodness-of-fit plots and visual predictive checks of the final model are depicted in Figure S3 and Figure S4. The observed unbound fraction versus individual predicted unbound fraction is depicted in Figure S5. The code describing the final model is provided at the end of this document.

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Table S1. Typical parameter values for the final isavuconazole model.

	Parameter estimate	Parameter estimate 95% confidence interval
Structural model		
F	41.0%	32.4%-50.8%
K_a	0.179 h^{-1}	0.110-0.280
CL_u	337 L/h	281-413
PHENO-CL_u	2.42	1.36-4.12
$V1_u$	2663 L	1696-3874
$V2_u$	26225 L	16748-38758
Q_u	1124 L/h	765.2-1577
B_{max}	12.8 mg/L	9.83-17.4
K_D	0.0806 mg/L	0.0544-0.128
Interindividual variability		
CL_u	23.7%	14.2%-36.8%
B_{max}	20.2%	11.2%-29.7%
Residual variability		
Proportional error (totalconcentrations)	20.8%	18.4%-24.5%
Proportional error (unbound concentrations)	43.5%	34.1%-56.4%

Abbreviations: F = absolute bioavailability; Ka = absorption rate constant; CL_u = unbound clearance; PHENO- CL_u = factor increase in unbound clearance in patient with concomitant phenobarbital use; $V1_u$ = unbound volume of distribution of the central compartment; $V2_u$ = unbound volume of distribution of the peripheral compartment; Q_u = unbound intercompartmental clearance; B_{max}: maximum binding capacity; K_D = dissociation constant.

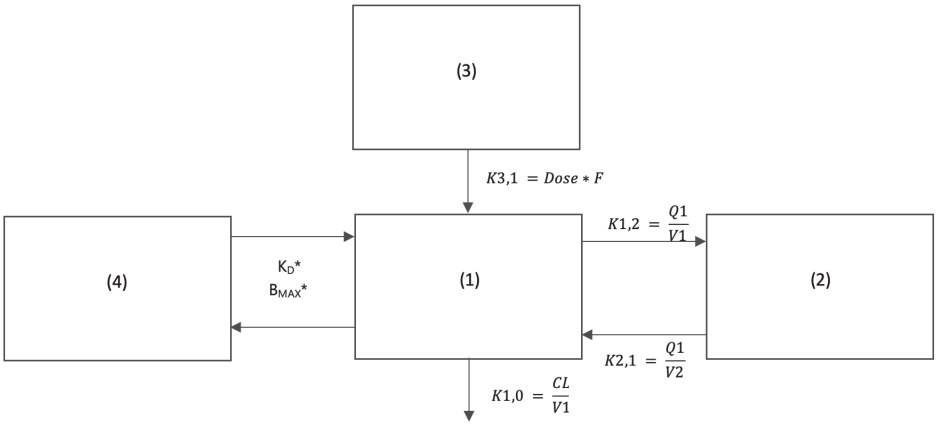

Figure S1. Schematic illustration of the final pharmacokinetic model of isavuconazole.

A two-compartment model with (1) = central compartment (for unbound concentrations); (2) = peripheral compartment (for unbound concentrations); (3) = dose compartment; (4) = compartment for total concentrations; K3,1 = rate constant of absorption; K1,0 = rate constant of elimination; K1,2 = rate constant of transfer from compartment 1 to compartment 2; K2,1 = rate constant of transfer from compartment 2 to compartment 1; CL = clearance; V1 = volume of distribution of compartment 1; V2 = volume of distribution of compartment 2; Q1 = intercompartmental CL; B_{max} = maximum binding capacity; K_D = dissociation constant.

*For total and unbound concentrations, a saturable protein binding model was implemented, as described previously.(4)

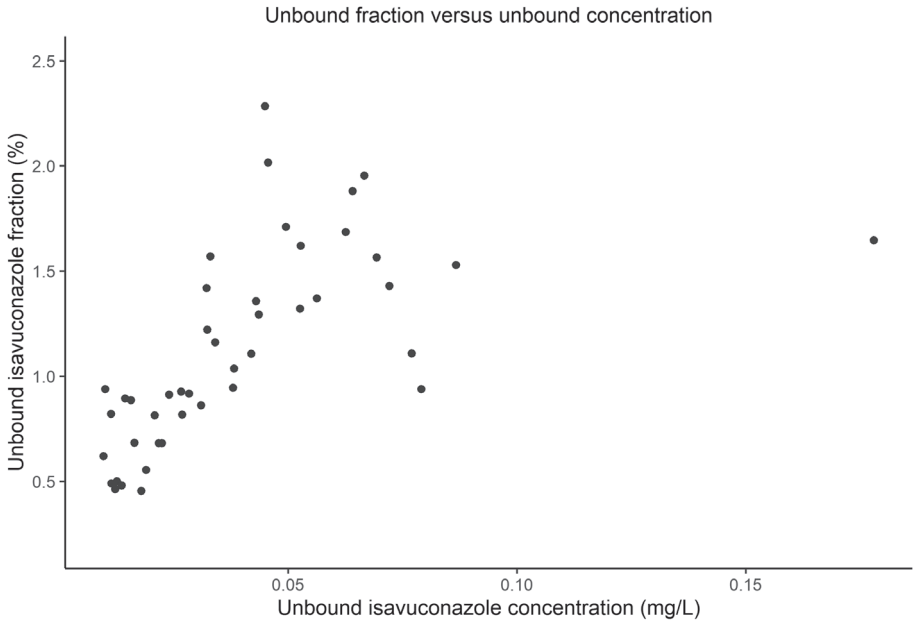

Figure S2. Observed unbound fraction versus unbound concentration.

Figure S3. Goodness-of-fit plots for the final model.

Total and unbound isavuconazole concentrations after intravenous (Ia, IIa, IIIa, IVa) and oral/nasogastric tube (Ib, IIb, IIIb, IVb) administration. Concentrations are logarithmically scaled.

I. Observed concentrations (mg/L) versus population-predicted concentrations (mg/L); The black line indicates the line of unity and the dashed line indicates the trend of the observations.
II. Observed concentrations in (mg/L) versus individual-predicted concentrations (mg/L); The black line indicates the line of unity and the dashed line indicates the trend of the observations.
III. Conditional weighted residuals versus population-predicted concentrations (mg/L); The black line indicates the line of unity and the dashed line indicates the trend of the observations.
IV. Conditional weighted residuals versus time after dose [TAD] (hours); The black line indicates the line of unity and the dashed line indicates the trend of the observations.

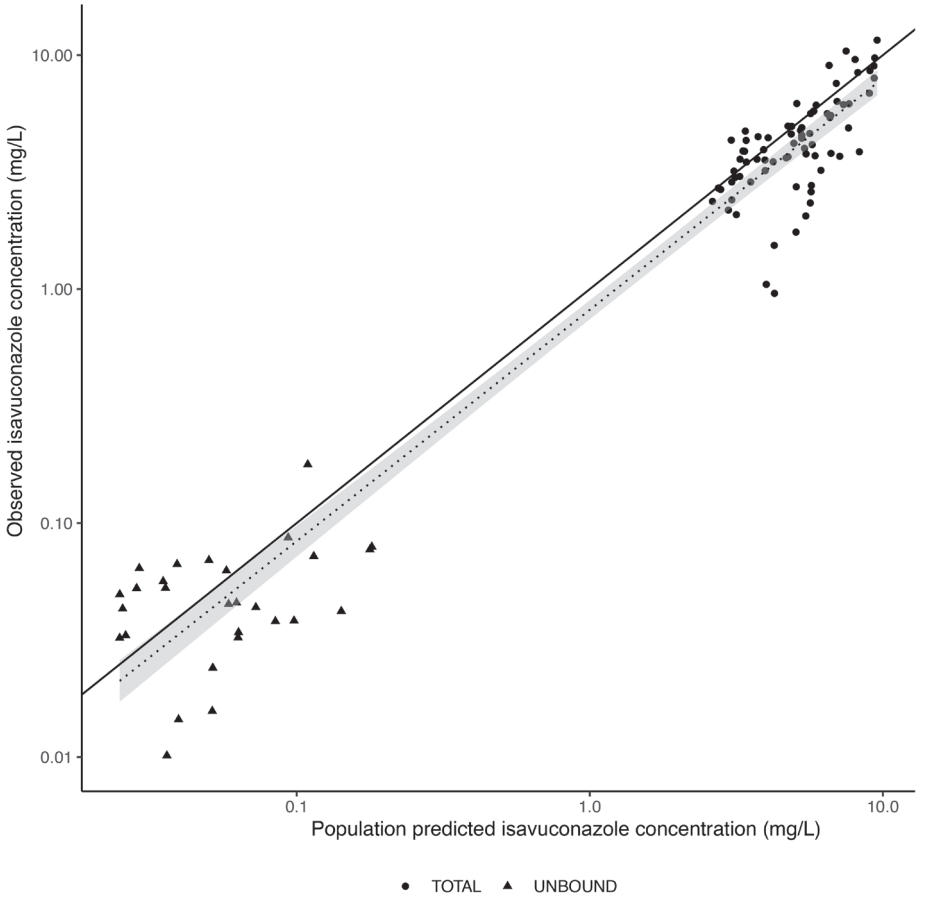
10.00
1.00
0.10
0.01
Observed isavuconazole concentration (mg/L)
0.1
1.0
10.0
Population predicted isavuconazole concentration (mg/L)
TOTAL
UNBOUND

Figure S3-Ia

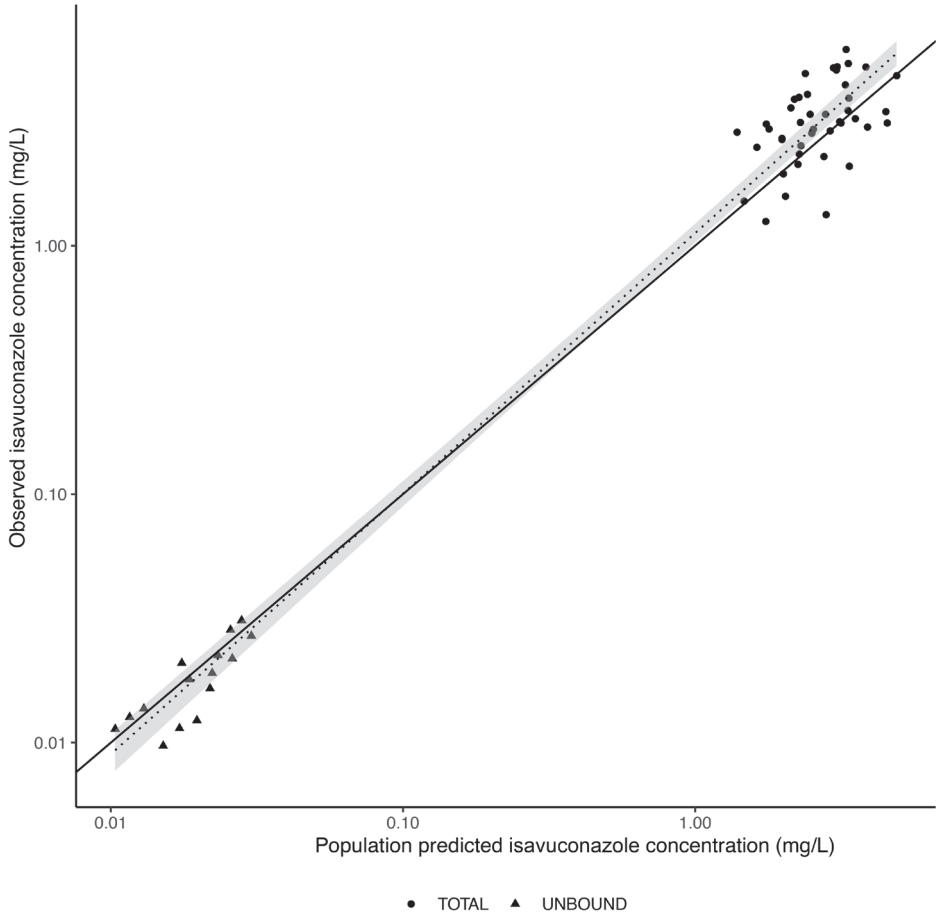
Observed isavuconazole concentration (mg/L)
1.00
0.10
0.01
0.01
0.10
1.00
Population predicted isavuconazole concentration (mg/L)
TOTAL
UNBOUND

Figure S3-Ib

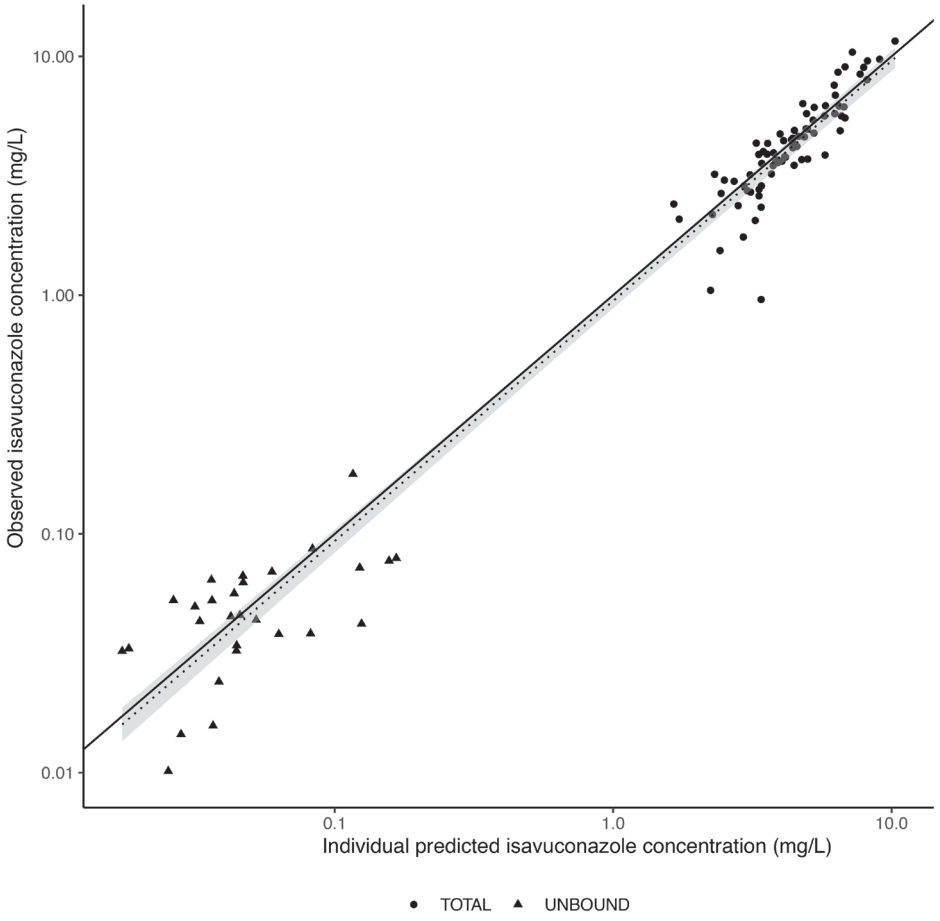

Figure S3-IIa

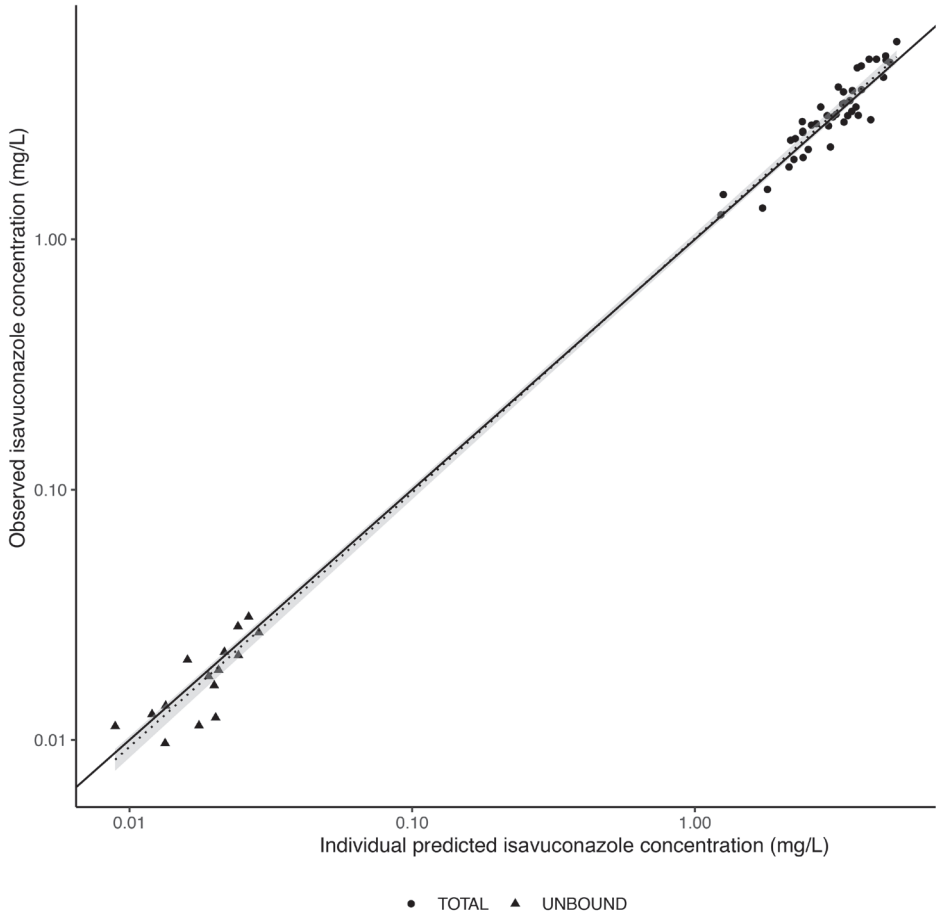

Figure S3-IIb

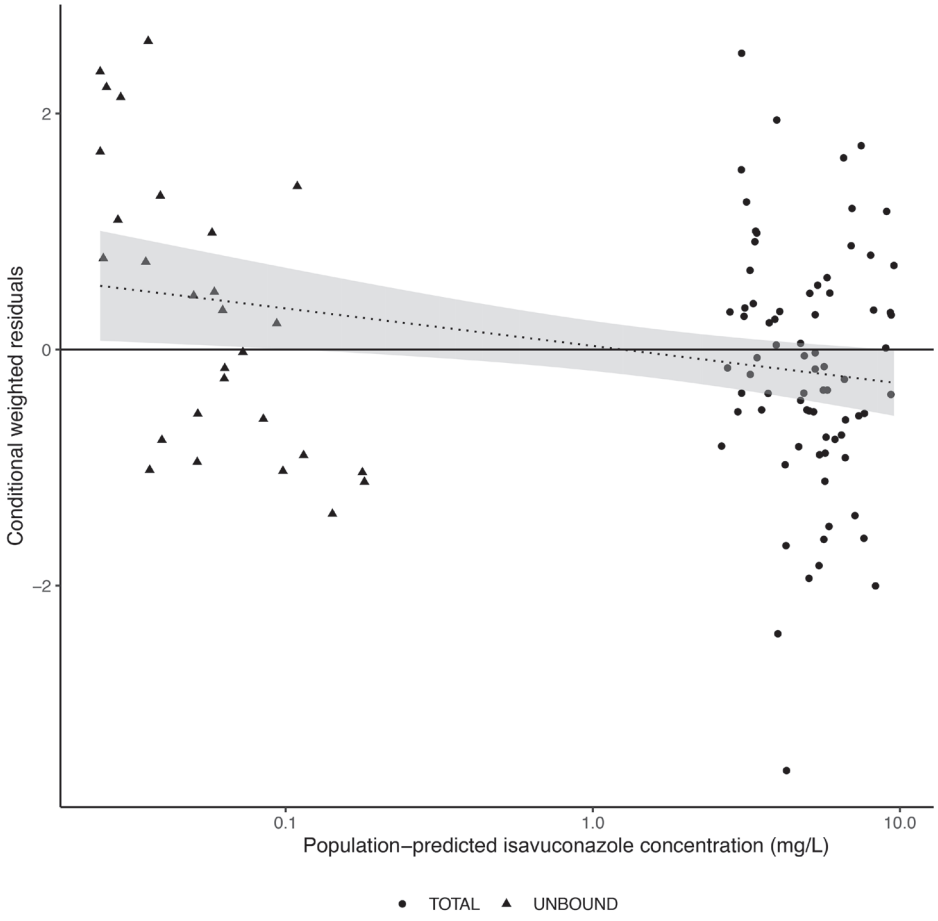

Figure S3-IIIa

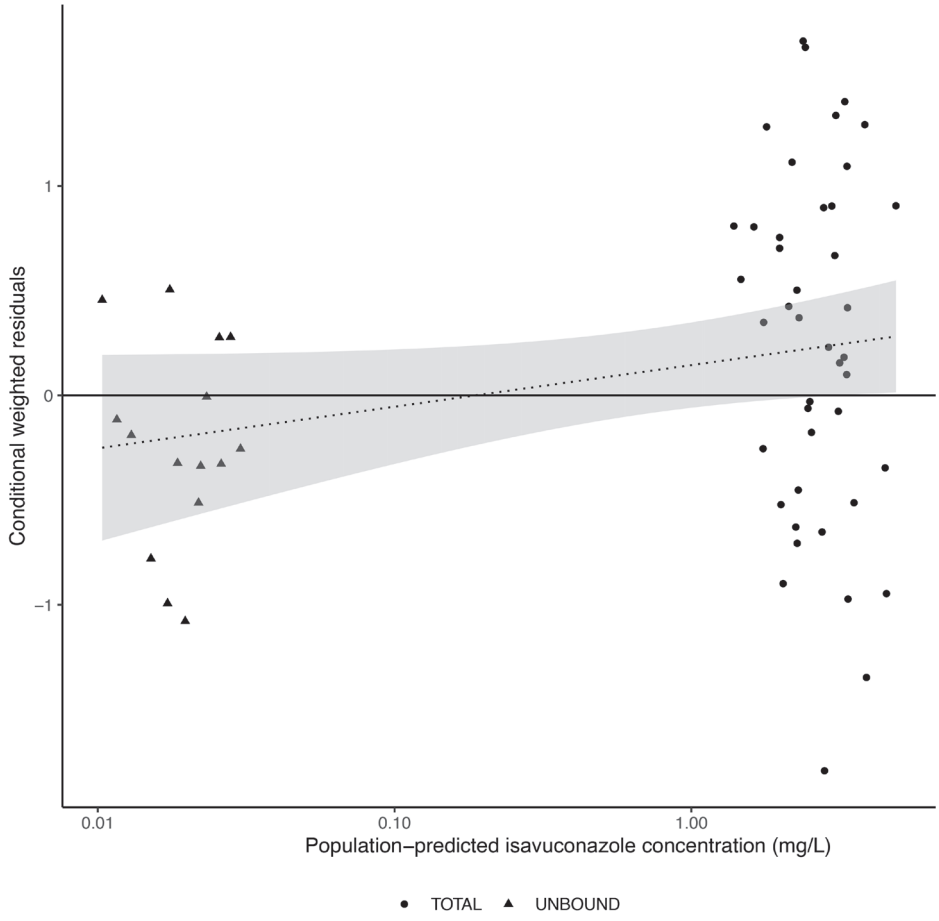

Figure S3-IIIb

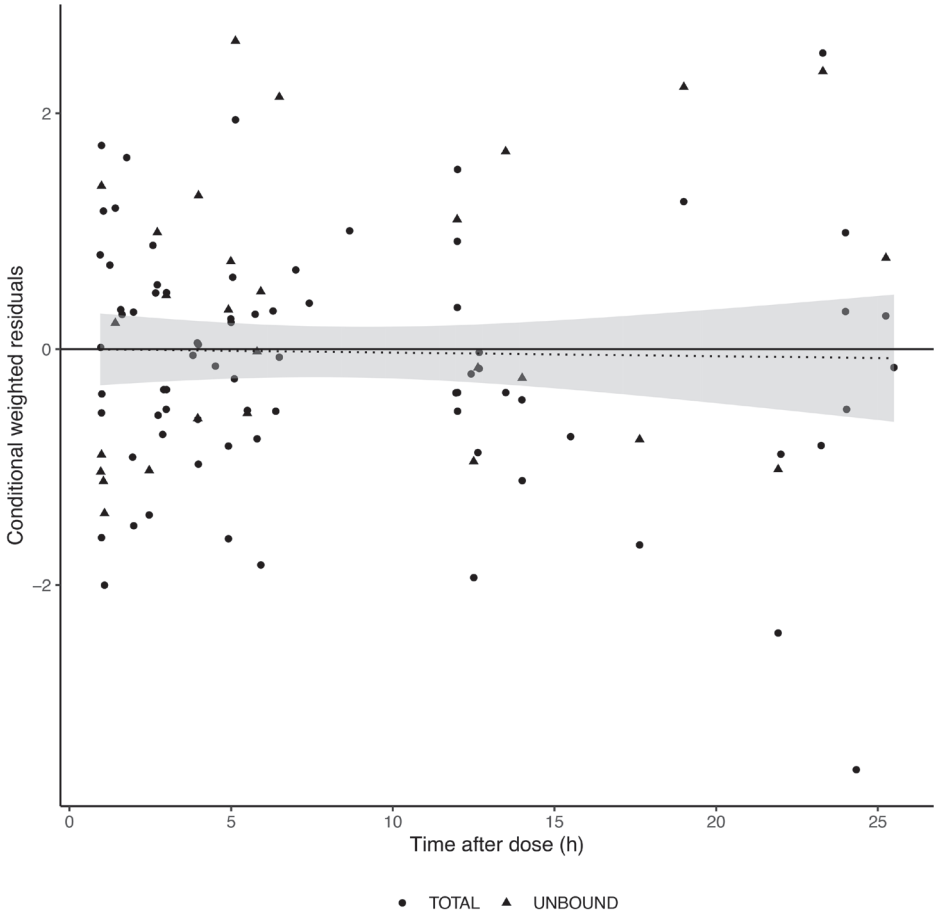

Figure S3-IVa

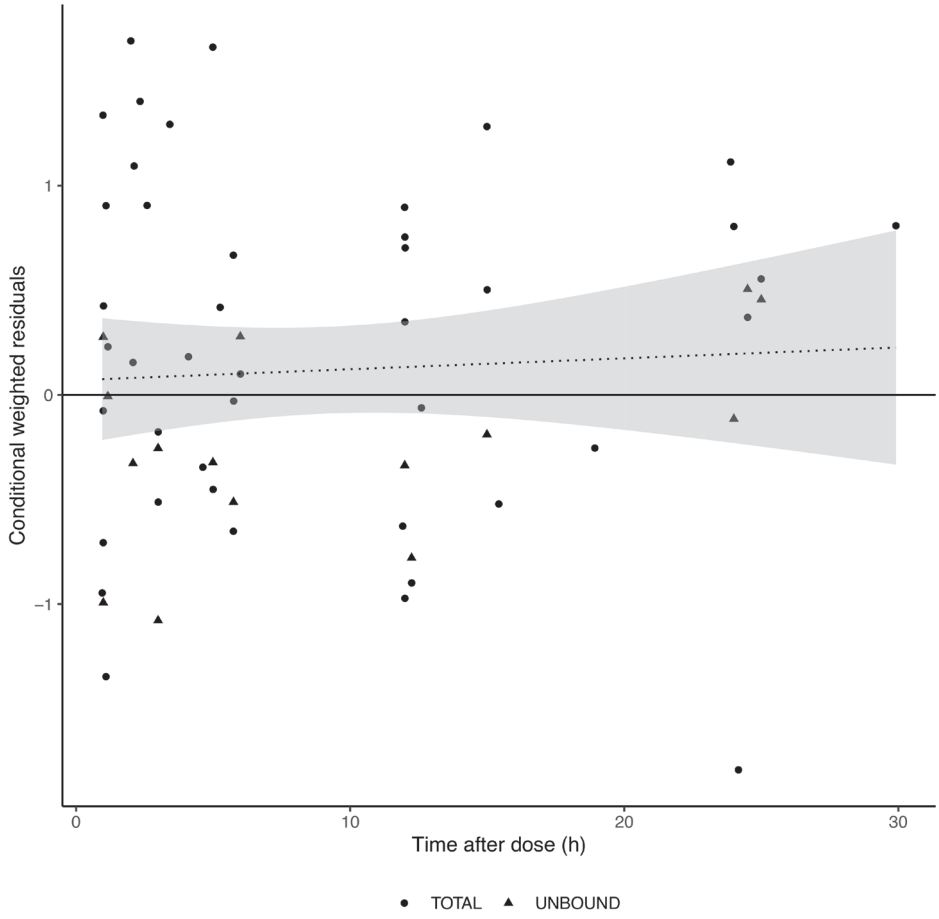

Figure S3-IVb

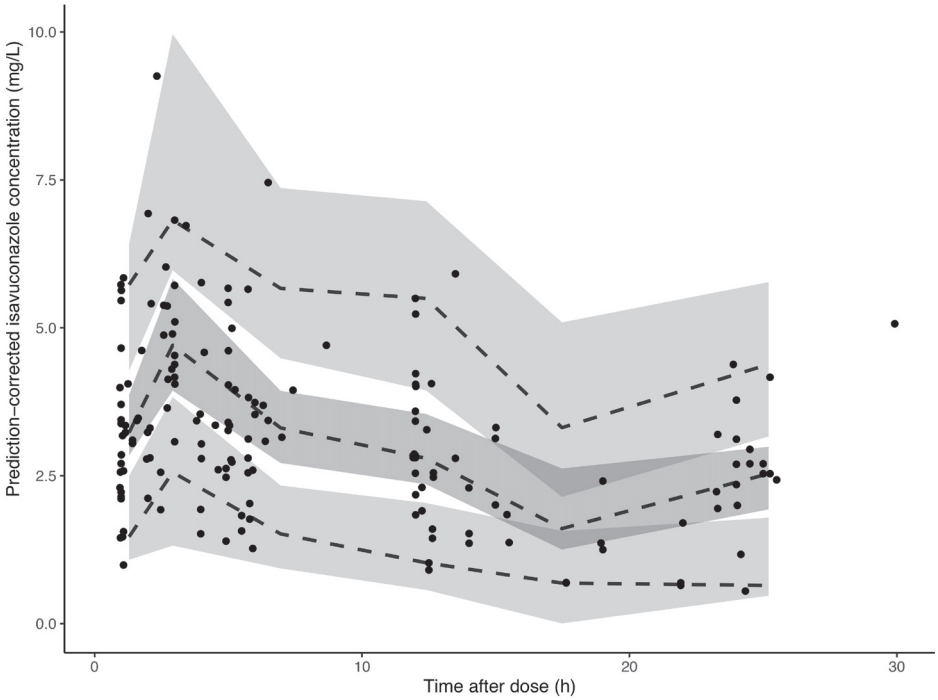

Figure S4. Prediction-corrected visual predictive check.

The black dots represent the observed isavuconazole concentrations. The shaded areas represent the 95% confident intervals of the simulation. The dashed lines represent the 5th, 50th and 95th percentile of the predicted isavuconazole concentrations. This figure indicates the similarity between the simulation and the observed data, as the percentiles lie within the confident intervals.

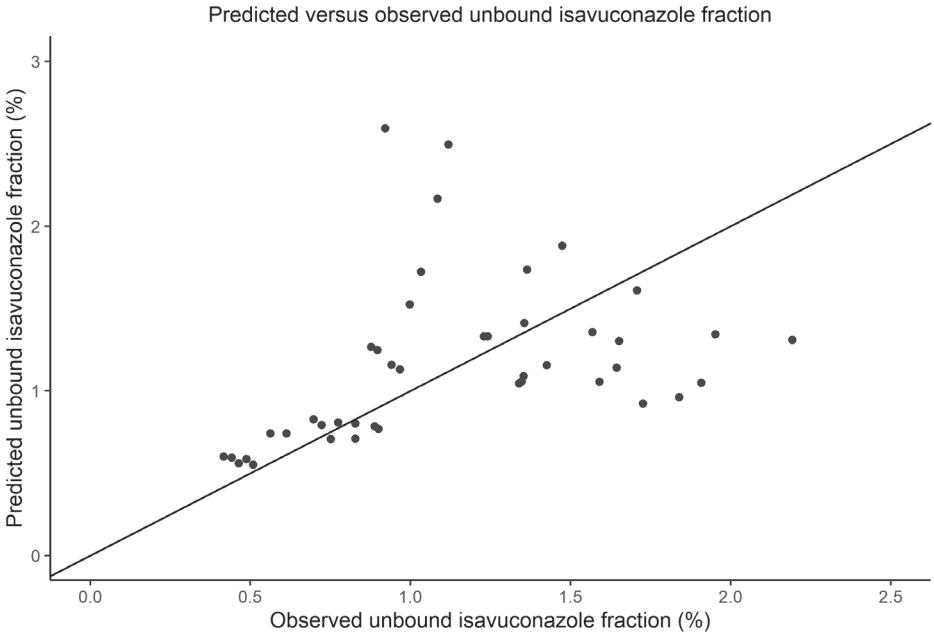

Figure S5. Observed unbound fraction versus individual predicted unbound fraction.
The black line indicates the line of unity.

NONMEM control stream for final model

```
$PROBLEM PK

$SUBROUTINES ADVAN5

$MODEL
COMP=(CENTRAL)
COMP=(PERI)
COMP=(DOSE)

$PK
FENO=0
IF (ID.EQ.1) FENO=1

;Time After Dose (TAD) calculation
IF (AMT.GT.0) THEN
DOSE=AMT
TDOS=TIME
ENDIF

TAD=TIME-TDOS

F3=THETA(1)* EXP(ETA(1))
KA = THETA(2) * ((WT/70)**(-0.25)) * EXP(ETA(2))
CL = THETA(3) * ((WT/70)**0.75) * (THETA(9)**FENO) * EXP(ETA(3))
V1 = THETA(4) * ((WT/70)**1)
Q  = THETA(5) * ((WT/70)**0.75)
V2 = THETA(6) * ((WT/70)**1)

S1 = V1

K31=KA
K12=Q/V1
K21=Q/V2
K10=CL/V1
$ERROR

CU=F                                    ; CALCULATES UNBOUND PK
BMAX = THETA (7) *EXP(ETA(4))           ; BMAX
KD = THETA(8)                           ; KD
CBOUND=((BMAX*CU)/(KD+CU))              ; PROTEIN BOUND CONCENTRATION

CTOT=CU+CBOUND                          ; TOTAL CONCENTRATION
FU=CU/CTOT                              ; FRACTION

IF (FREE.EQ.1) IPRED=CTOT
IF (FREE.EQ.2) IPRED=CU

IF (FREE.EQ.1) Y=IPRED+IPRED*ERR(1); RESIDUAL ERROR MODEL TOTAL
IF (FREE.EQ.2) Y=IPRED+IPRED*ERR(2); RESIDUAL ERROR MODEL UNBOUND

$THETA

(0, 0.41) ; F3
```

```
(0, 0.179) ; KA
(0, 337) ; CL
(0, 2660) ; V1
(0, 1120) ; Q
(0, 26200) ; V2
(0, 12.8) ; BMAX
(0, 0.0806) ; KD
(0, 2.42) ; FENO-CL

$OMEGA
 0 FIX  ; F3
 0 FIX  ; KA
 0.0561 ; IIV CL
 0.0407 ; IIV BMAX

$SIGMA
 0.0432 ; PROP ERR TOTAL
 0.189 ; PROP ERR UNBOUND
$EST METHOD=1 INTER MAXEVAL=2000 NOABORT SIG=3 PRINT=1
$COV MATRIX=R PRINT=E
```

Table S2. Indication specifics

Patient ID	Categorization according to EORTC/MSG criteria*	Localization fungal disease	Type of infection (species)
1	Proven	Pulmonal, cerebral	Mucormycosis (Rhizopus microsporus)
2	Probable	Pulmonal	Mucormycosis
3	Proven	Pulmonal, cerebral	Mucormycosis (Rhizomucor pusillus)
4	NA (prophylaxis)	x	x
5	Possible	Pulmonal	Not specified
6	Probable	Pulmonal (*Aspergillus*/ *Fusarium*), sinus (*Fusarium*), skin (*Fusarium*), systemical (*Fusarium*)	Aspergillosis (mixed infection with *Fusarium*)
7	Proven	Pulmonal	Mucormycosis (Rhizomucor pusillus)
8	Probable	Pulmonal, cerebral	Mucormycosis
9	Proven	Kidney en ureter	Mucormycosis (Rhizopus microsporus)
10	Possible	Pulmonal, cerebral	Not specified
11	Possible	Pulmonal	Not specified
12	Possible	Pulmonal	Not specified
13	Probable	Pulmonal	Aspergillosis
14	Probable	Pulmonal	Aspergillosis
15	Proven	Pulmonal, skin	Mucormycosis (Absidia species)
16	Possible	Pulmonal	Not specified
17	Probable	Pulmonal	Aspergillosis

Abbreviations: EORTC/MSG = European Organization for Research and Treatment in Cancer/ Mycoses Study
Group; NA = not applicable.
*EORTC/MSG 2008 criteria.

CHAPTER 5

PHARMACOKINETIC EVALUATION OF TWICE-A-WEEK MICAFUNGIN FOR PROPHYLAXIS OF INVASIVE FUNGAL DISEASE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA: A PROSPECTIVE OBSERVATIONAL COHORT STUDY

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J Antimicrob Chemother. 2022 Feb 23;77(3):699-703

Abstract

Objectives

To determine the pharmacokinetics of twice-a-week micafungin prophylaxis in paediatric leukaemic patients to provide the rationale for this approach.

Methods

Twice-a-week micafungin at a dose of 9 mg/kg (maximum 300 mg) was given during the leukaemic induction treatment with at least one pharmacokinetic assessment. Non-linear mixed-effects modelling was used for analysis. For model building, our paediatric data were strengthened with existing adult data. Monte Carlo simulations were performed with twice-a-week dosing regimens of 5, 7 and 9 mg/kg and flat dosing per weight band. Simulated paediatric exposures were compared with the exposure in adults after a once-daily 100 mg regimen.

Results

Sixty-one paediatric patients were included with a median age and weight of 4.0 years (range 1.0–17) and 19.5 kg (range 8.60–182), respectively. A two-compartment model best fitted the data. CL and central Vd were lower ($P<0.01$) in paediatric patients compared with adults. Predicted exposures (AUC0–168) for the 5, 7 and 9 mg/kg and flat dosing per weight band regimens exceeded the adult reference exposure.

Conclusions

All twice-a-week regimens appeared to result in adequate exposure for *Candida* therapy, with simulated exposures well above the adult reference exposure. These findings provide the rationale for the pharmacokinetic equivalence of twice-a-week and once-daily micafungin regimens. The greater micafungin exposures seem to be caused by a slower-than-anticipated CL in our paediatric leukaemic patients. The generalizability of our results for *Aspergillus* prophylaxis cannot be provided without assumptions on target concentrations and within-class identical efficacy.

Introduction

Invasive fungal disease is one of the most common causes of treatment-related mortality in paediatric haemato-oncology patients.[1] Fungal prophylaxis during the induction treatment for paediatric patients with ALL may be required depending on regional incidence of invasive fungal disease. There are limited antifungal drugs available that can be safely deployed in the early phase of ALL treatment. The preferred drugs of choice are the mould-active azoles, but they are relatively contraindicated due to their drug–drug interaction profile. The drug–drug interaction with the weekly administered chemotherapeutic agent vincristine is especially difficult to manage.[2] Echinocandins appear to be a safe choice in this setting. As their β-d-glucan synthase target is unique to fungi, echinocandins are generally well tolerated and show minimal drug–drug interactions. Echinocandins show activity against both *Candida* and *Aspergillus* species.[3] In a recent large randomized open-label trial in paediatric patients with AML, the efficacy of caspofungin for prophylaxis of invasive fungal disease, including invasive aspergillosis, was demonstrated.[4]

The drawback of a prophylactic strategy with echinocandins is the customary daily IV dosing. To overcome the need for daily hospital visits, a twice-a-week dosing regimen might be a preferable strategy. Such a strategy was explored in adults based on a bio-equivalency approach for both anidulafungin and micafungin. A three-times higher dose of these drugs in a twice-a-week regimen resulted in a comparable exposure to the equivalent daily dose.[5, 6] These results provide the pharmacokinetic rationale to study a twice-a-week micafungin regimen in paediatric patients.

Three studies have explored intermittent micafungin regimens of 3 mg/kg every 48 h, 3–4 mg/kg twice-a-week or 5 mg/kg twice-a-week in paediatric patients, either as a single dose or multiple doses.[7-9] In these studies, dose selections and recommendations were made based on targets that were directly translated from the minimum effective concentrations or minimum inhibitory concentrations, dependent on the species.[7-9] Although these studies provided valuable pharmacokinetic information, sample sizes were relatively small and the choices made for pharmacokinetic targets and dose recommendations can be debated. There remains a clinical need for population pharmacokinetic information from a large cohort of patients with multiple dosing to support a twice-a-week regimen in paediatric patients.

Here, the feasibility of a patient-friendly prophylactic regimen for invasive fungal disease was explored by giving micafungin in a twice-a-week regimen at a dose of 9 mg/kg/administration during the induction treatment of childhood ALL. During this period

we evaluated the pharmacokinetics of this micafungin dosing strategy, developed an integrated population pharmacokinetic model for children and adults, and simulated various dosing regimens that could be used as prophylactic regimens for invasive fungal disease.

Methods

Patients and study

All paediatric patients aged <18 years and diagnosed with childhood ALL received micafungin prophylaxis as part of standard care during the first 5 weeks of their induction treatment in the Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands. This study was an observational, prospective pharmacokinetic cohort study, which was conducted between September 2018 and April 2019. Patients who signed consent for the Dutch childhood oncology group (DCOG) ALL-11 protocol were eligible for this evaluation. The evaluation protocol was approved by the Medical Ethics Committee Erasmus MC of Rotterdam (MEC-2018-1684).

Micafungin dosing and sampling

As part of clinical practice in the Princess Máxima Center for Pediatric Oncology, a twice-a-week prophylactic micafungin regimen at a dose of 18 mg/kg/week (9 mg/kg/administration; maximum 300 mg) was chosen based on a bio-equivalence approach.[5, 6] The dose was chosen as follows: the paediatric micafungin dose for treatment of invasive candidiasis or candidaemia is 2–4 mg/kg/day.[10] Hence, a dose between 14 and 28 mg/kg/week divided over two administrations could be a logical approach. The pragmatic decision was made to choose a dose of 18 mg/kg/week and thus a dose of 9 mg/kg/administration in a twice-a-week regimen. Regarding the toxicity profile of micafungin, once-daily doses of up to 8 mg/kg were well tolerated in adults and once-daily doses of up to 15 mg/kg were administered in the neonatal populations without signs of severe toxicity.[11-13] The chosen micafungin dose of 9 mg/kg/administration was therefore expected to be well tolerated. The infusion time was 2 h per dose. The twice-a-week dosing schedule was chosen at the discretion of the physician. As part of routine care, patients were monitored for micafungin exposure to prevent unexpected toxic exposures. Pharmacokinetic samples were obtained as early in the treatment as possible, after patients had a venous indwelling catheter inserted. A five-point micafungin curve was obtained from patients via indwelling venous catheter sampling. Venous blood samples (2.0 mL) were obtained at t=0 (before start of the micafungin infusion), t=2 h (at the end of infusion) and t=4, 5 and 24 h after the start of micafungin infusion.

Clinical and laboratory assessments

Baseline characteristics such as sex, age, height and total body weight were extracted from the electronic health record system. Micafungin-related data such as dose, infusion time, dosing interval, dose adjustments, times of blood sampling and micafungin concentrations were extracted from the electronic health record system and by means of a dedicated laboratory form.

Bioanalysis

Micafungin concentrations were measured with a validated UPLC fluorescence method. This method was validated over a concentration range of 0.01–32 mg/L. The accuracy of the assay ranged from 97.6% to 101.6%, interday precision ranged from 0.7% to 2.2% and intraday precision ranged from 1.4% to 5.1%.

Pharmacokinetic analysis

The collected paediatric pharmacokinetic data were combined with previously collected pharmacokinetic data of micafungin in adult haematology patients, from our group, for purposes of data enrichment and improvement of model robustness.[5] This allowed for a direct comparison of pharmacokinetics between paediatric ALL patients and adult haematology patients.

The pharmacokinetics of micafungin were analysed using non-linear mixed-effects modelling (NONMEM) with the software package NONMEM v7.4.1. The covariate model included a priori allometrically scaled CL and volume of distribution (V_d) to a fat-free mass (FFM) of 57.2 kg, corresponding to the mass of a typical male patient of 1.80 m.[14] Furthermore, a binary covariate was added for paediatric and adult patients. Model evaluation was assessed by standard goodness-of-fit plots and prediction-corrected visual predictive checks. The details of the analysis and model evaluation are described in the Supplementary data, available at JAC Online.

Alternative dose evaluation

The final pharmacokinetic model was used to explore different dosing regimens by means of Monte Carlo simulations. For this purpose, extraction of demographic data of paediatric ALL patients from the database of the DCOG was performed. Four different dosing regimens were simulated: micafungin twice-a-week regimens of 5, 7 and 9 mg/kg, with a maximum of 300 mg per dose, and a flat dosing regimen per weight band. The 5 and 7 mg/kg dosing regimens were chosen based on earlier studies and at the discretion

of the researchers, respectively.[7, 9] Additionally, we chose an allometric dosing strategy with a flat dose for each weight band to take optimal benefit of vial sizes (50 mg per vial) and allow a practical dosing strategy. The doses per weight band were categorized as follows: <20 kg received 100 mg, 20–40 kg received 150 mg and >40 kg received 300 mg.

Predicted paediatric micafungin exposures of all four regimens were compared with a reference micafungin exposure in adult haematology patients after daily administration of 100 mg micafungin given for either *Candida* prophylaxis or treatment.[5] The pragmatic decision was made to at least attain the adult reference exposure for *Candida* infections in the absence of clinical breakpoints for *Aspergillus* infections.

Results

Patient characteristics

A detailed description of patient characteristics of our paediatric population and the adult population,[5] as presented earlier, is given in Table 1. A total of 61 paediatric ALL patients were evaluated in this study, of which 55.7% were male. Median age and weight were 4.0 years (range 1.0–17) and 19.5 kg (range 8.60–182), respectively, for the paediatric cohort. The median micafungin dose was 175 mg (range 77–300). Pharmacokinetic samples were obtained after first and multiple administrations (range 1–8 administrations) of micafungin. In total, 73 micafungin sampling occasions occurred. A full four- or five-point pharmacokinetic curve was taken on 49 sampling occasions, and ≤3 concentrations were taken on 24 sampling occasions.

Pharmacokinetic analysis

Data of 61 paediatric patients and 20 adult patients were used for pharmacokinetic analysis. Combining both paediatric and adult cohorts resulted in a total of 760 paired observations of time and micafungin plasma concentrations. In short, the pharmacokinetics of micafungin were best described using a two-compartment linear pharmacokinetic model. The details of the analysis can be found in the Supplementary data (including Table S1 and Figures S1–S3b). It was found that the allometrically scaled CL and V_d of micafungin in paediatric patients were significantly lower ($P<0.01$) compared with adult haematology patients, with a respective $CL_{paediatrics}$ of 0.678 (95% CI 0.634–0.725) versus CL_{adults} of 1.02 L/h (95% CI 0.913–1.13) and $V_{d,paediatrics}$ of 7.91 (95% CI 6.51–9.27) versus $V_{d,adults}$ of 11.6 L (95% CI 9.45-13.9).

Table 1. Patient characteristics of the paediatric ALL cohort and the adult haematology cohort

Characteristic	Paediatric patients	Adult patients[a]
Number of patients, N	61	20
Sex (%)		
Male	55.7	60.0
Female	44.3	40.0
Age, years; median (range)	4.0 (1.0–17)	59.5 (38–68)
Weight, kg; median (range)	19.5 (8.60–182)	86.6 (53.5–110.1)
Height, cm; median (range)	107 (75.0–200)	178 (152–189)
Underlying malignancy, n		
ALL	61	—
AML/MDS	—	15
Other	—	5
Treatment, n		
Induction chemotherapy	61	—
Allogeneic HSCT	—	10
Remission-induction chemotherapy		10
Micafungin dose, mg; median (range)		
Daily	—	100
Twice weekly	175 (77–300)	300
Number of samples, N	262	498
Number of occasions with a full 4- or 5-point PK curve, n	49	—
Number of occasions with ≤3 micafungin concentrations, n	24	—

MDS, myelodysplastic syndromes; PK, pharmacokinetics.
[a]Data from Muilwijk et al.[5]

Alternative dose evaluation

Details on the demographics of the real-life paediatric ALL cohort are given in Table 2. The predicted micafungin exposures are presented in Figure 1. The median predicted micafungin exposures ($AUC_{0–168\,h}$) of twice-a-week 5, 7 and 9 mg/kg regimens and a flat dosing regimen were, respectively, 800 (IQR 652–987), 1069 (IQR 882–1293), 1311 (IQR 1071–1576) and 979 mg·h/L (IQR 802–1191). All four regimens showed an above-median exposure compared with the median exposure of 690 mg·h/L (IQR 583–827) in adult haematology patients after a daily dose of 100 mg.

Table 2. Demographics of a real-life cohort of paediatric patients with ALL used for dose exploration simulations

Demographic	
Number of patients, N	590
Sex (%)	
Male	59.3
Female	40.7
Age, years; median (range)	5.0 (1.0–17)
Weight, kg; median (range)	20.0 (8.70–105)
Height, cm; median (range)	114 (75.0–196)

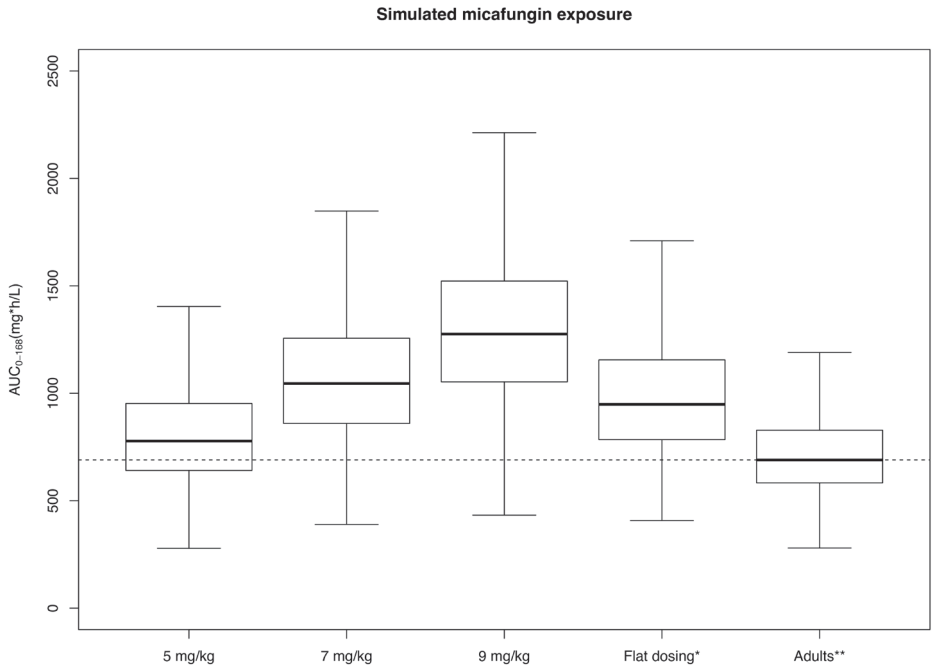

Figure 1. Predicted micafungin exposure of four twice-a-week paediatric regimens compared with a daily regimen in adult patients.

The dashed line represents the median exposure in adult haematology patients. *Flat dosing per weight band: weight bands were categorized as follows: <20 kg received 100 mg, 20–40 kg received 150 mg and >40 kg received 300 mg. **Adult haematology patients received a daily dose of 100 mg micafungin.

Discussion

In this study the pharmacokinetics of micafungin were evaluated in the largest cohort to date and at multiple doses in a twice-a-week regimen for the purpose of fungal prophylaxis in paediatric ALL patients.

Interestingly, a significantly lower micafungin CL and V_d were found in paediatric ALL patients compared with adult haematology patients, despite allometric scaling. Very little information to explain this observation was found in the literature. Four earlier studies reported the population pharmacokinetics of micafungin in paediatric patients.[9, 15-17] As these studies used different covariates and scaling methods, we could not directly compare their parameter estimates with the parameter estimates found in our model. Three of these studies combined or compared their paediatric data with adult data. Neither of these studies reported any differences in pharmacokinetic parameters or exposures between paediatric patients and adults after adjustment for weight, with or without allometric scaling.[15-17] A non-compartmental analysis reported a significantly higher weight-adjusted CL in paediatric patients aged <8 years compared with paediatric patients aged >8 years and adult patients.[18] This study did not take allometry into account, which could explain the higher weight-adjusted CL reported in the younger group of patients.

Our initial assumption was that paediatric patients have reduced CL due to concomitant hepatotoxic chemotherapy and subsequently reduced hepatic enzyme function. Micafungin is metabolized by arylsulfatase and catechol-O-methyltransferase and altered enzyme function might lead to changes in micafungin metabolism and CL.[19] Yet, in adult patients with mild to severe hepatic impairment no changes in pharmacokinetic parameters were observed.[20, 21] This makes our hypothesis less likely and a final explanation for this observation remains to be unravelled.

A twice-a-week regimen can be considered at least comparable to a daily regimen in terms of exposure, as the predicted median micafungin exposure in all simulated dosing regimens exceeded the reference median micafungin exposure in adult haematology patients.

Although the place of a twice-a-week micafungin regimen for *Candida* prophylaxis seems appropriate given the chosen target exposure, the place of this micafungin regimen in the setting of *Aspergillus* prophylaxis can be debated. Recently, caspofungin was reported to be effective for prophylaxis of invasive aspergillosis in paediatric patients.[4] We are of the opinion that micafungin will likely have similar efficacy as caspofungin. These thoughts

are supported by the report that 50 mg micafungin therapy resulted in a trend towards a lower incidence of *Aspergillus* infections.[22] We could hypothesize that aiming for a target exposure of a twice-a-week micafungin regimen that is at least similar to a 100 mg daily exposure would mark comparable clinical efficacy of these regimens. Evidently, more knowledge on the pharmacodynamics of micafungin for prophylaxis of *Aspergillus* infections will be needed to substantiate our hypothesis. Caution should be exercised to interpret our findings, as it remains challenging to recommend a specific dosing regimen in the absence of these clinical targets for *Aspergillus* infections. The efficacy of the twice-a-week 9 mg/kg regimen is currently under evaluation for *Aspergillus* prophylaxis.

The twice-a-week regimens of 5 and 7 mg/kg and flat dosing by weight band might be alternative strategies as these regimens result in analogous exposure compared with the adult reference daily regimen (Figure 1). These assumptions only hold their strength when linear pharmacokinetics are foreseeable. So far, no evidence is available supporting non-linear pharmacokinetics of micafungin. The efficacy of either regimens remains a topic of investigation.

In conclusion, the pharmacokinetic data obtained from this large combined paediatric and adult population will support the rationale of a twice-a-week micafungin regimen. Our analysis proved that a twice-a-week micafungin regimen is at least pharmacokinetically equivalent to a daily regimen. Understanding the underlying mechanism of the lower CL in paediatric ALL patients and the clinical targets of micafungin for *Aspergillus* infections will help to improve this twice-a-week micafungin dosing strategy for prophylaxis of invasive fungal disease.

Acknowledgement

Part of these results were presented in the online European Congress of Clinical Microbiology and Infectious Diseases 2020 Abstract Book. Abstract number: 4800.

Author contribution statement

D.B., W.J.E.T., T.F.W.W. and R.J.M.B. designed the research; D.B. performed the research; D.B., R.t.H. and R.J.M.B. analysed data; D.B. and R.J.M.B. wrote the manuscript; R.t.H., W.J.E.T., T.F.W.W. and E.W.M. provided critical revision of the manuscript. All authors provided approval of the final version.

Transparency declarations

No conflicts of interest/competing interests are applicable for this work. Disclosures outside of this work: R.J.M.B. has served as a consultant to Astellas Pharma, Inc., F2G, Amplyx, Gilead Sciences, Merck Sharp & Dohme Corp., Mundipharma and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharp & Dohme Corp. and Pfizer, Inc. All contracts were through Radboudumc and all payments were invoiced by Radboudumc. None of the other authors have any conflicts to declare.

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Supplementary file

Description of the final model

The PK of micafungin were analysed using nonlinear mixed effects modelling (NONMEM), with the software package NONMEM V7.4.1 including Piraña v2.9.7 as an interface for NONMEM, R statistics v4.0.3 and Perl Speaks NONMEM. A two-compartment model, with intravenous administration and linear elimination was used as a starting point for model building. Adding a third compartment did not significantly decrease the objective function or goodness-of-fit plots. CL and Vd were allometrically scaled with fixed exponents of 0.75 and 1, respectively, to a fat-free mass (FFM) of 57.2 kg, corresponding to the mass of a typical male patient of 1.80 m and 70kg[1]. When scaling CL, V1, V2 and Q1 to 57.2 kg, the objective function significantly decreased. As some patients were sampled at multiple occasions, inter-occasion variability (IOV) was incorporated in the structural model to minimize potential bias in parameter estimates[2] and improved model fit best when introduced on CL. Interindividual variability (IIV) was added on CL, V1 and Q1. Furthermore, correlations between IIVs of parameter estimates were assessed and subsequently incorporated in the model for CL and V1. The first-order conditional estimation (FOCE) method was used for model building. Distributions of interindividual random effects were assumed to be log-normally distributed. A proportional error model was used to describe the residual error, with a separate error model for the adult and paediatric dataset. Parameter uncertainty was assessed with Sampling Importance Resampling (SIR)[3].

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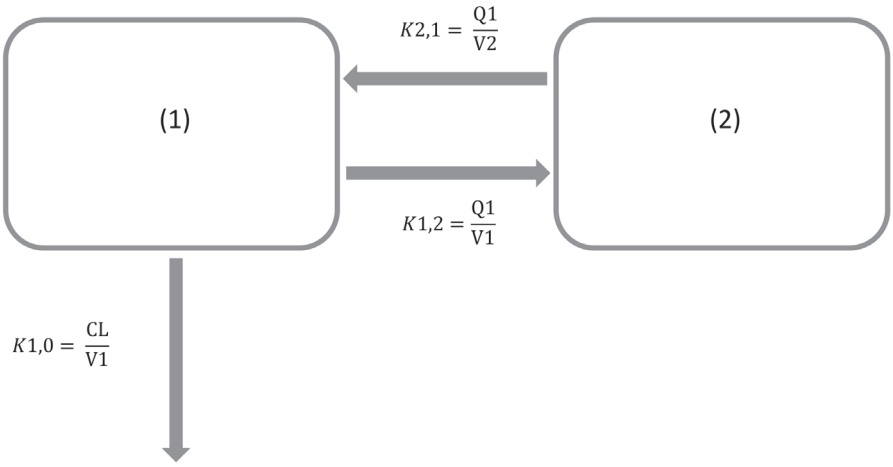

Figure S1. Schematic illustration of the final pharmacokinetic model of micafungin.

A two-compartment model with (1) = central compartment; (2) =peripheral compartment (2); K1,0 = rate constant of elimination; K1,2 = rate constant of transfer from compartment 1 to compartment 2; K2,1 = rate constant of transfer from compartment 2 to compartment 1; CL= clearance; V1 = volume of distribution of compartment 1; V2 = volume of distribution of compartment 2; Q = intercompartmental CL.

Table S1. Parameter estimates of the final model

	Estimate	**CI 95%**
Structural model		
CL (paediatric patients)	0.678 L/h	0.634-0.725
CL (adult patients)	1.02 L/h	0.913-1.13
V1 (paediatric patients)	7.91 L	6.51-9.27
V1 (adult patients)	11.6 L	9.45-13.9
V2	9.01 L	8.10-10.0
Q1	3.50 L/h	2.58-4.53
Interindividual variability		
CL	24.9%	18.9%-28.6%
V1	34.3%	25.5%-42.7%
Correlation CL-V1	87.3%	45.7%-100%
Q1	70.6%	52.4%-86.8%
Intraindividual variability		
CL (paediatric/adult patients)	10.1%	7.8%-12.0%
Residual variability		
Proportional error (paediatric patients) Proportional error (adult patients)	9.0% 12.1%	7.5%-10.4% 11.1%-13.0%

Abbreviations: CL = clearance; V1 = volume of distribution of the central compartment; V2 = volume of distribution of the peripheral compartment; Q1 = intercompartmental clearance; CI = confidence interval.

Model evaluation

The goodness-of-fit plots are shown in supplementary Figure S2 (panel A-D). Observed concentrations were plotted versus population-predicted (A) and individual-predicted concentrations (B). Conditional weighted residuals were plotted versus population-predicted concentrations (C), time after dose (D). These figures show that the data is well described by the model. Both at a population level (A) and at an individual level (B) the data is well described by the model, as the trend of the observations lies closely to the line of unity. The conditional weighted residuals were evenly scattered around zero in the plots versus population-predicted concentrations (C) and time after dose (D). Furthermore, the majority of data points lie within the -2 to 2 interval. This indicates a good fit of the model.

Goodness of fit plots

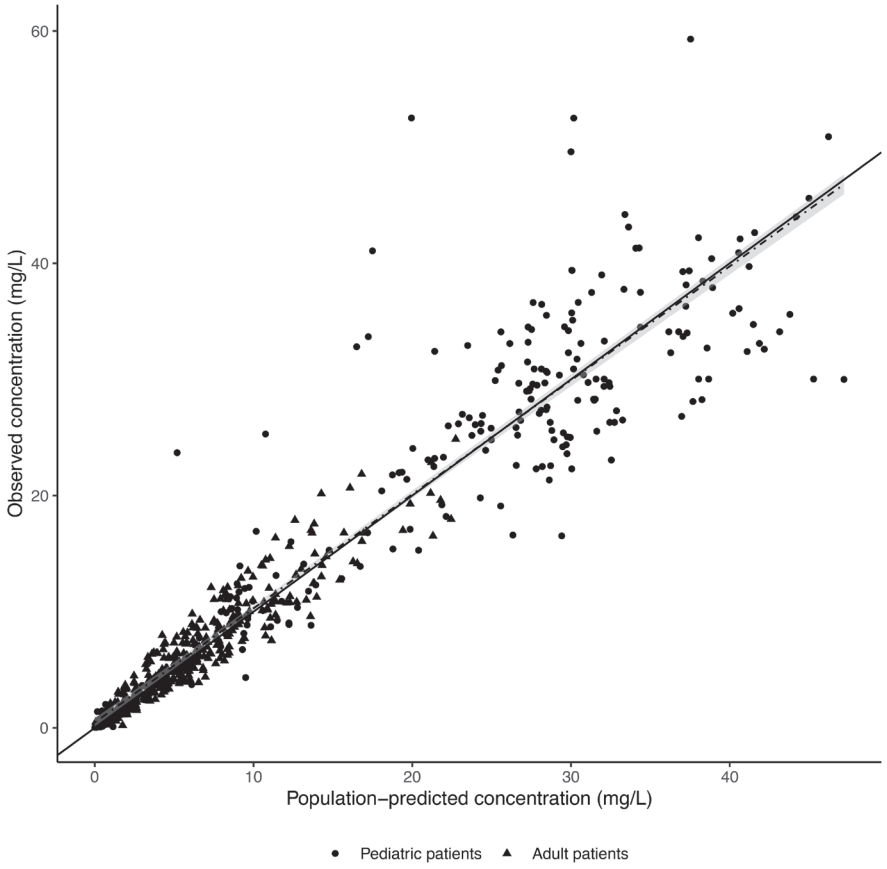

Figure S2A. Observed concentration versus population-predicted concentration.
The black line indicates the line of unity and the dashed line indicates the trend of the observations.

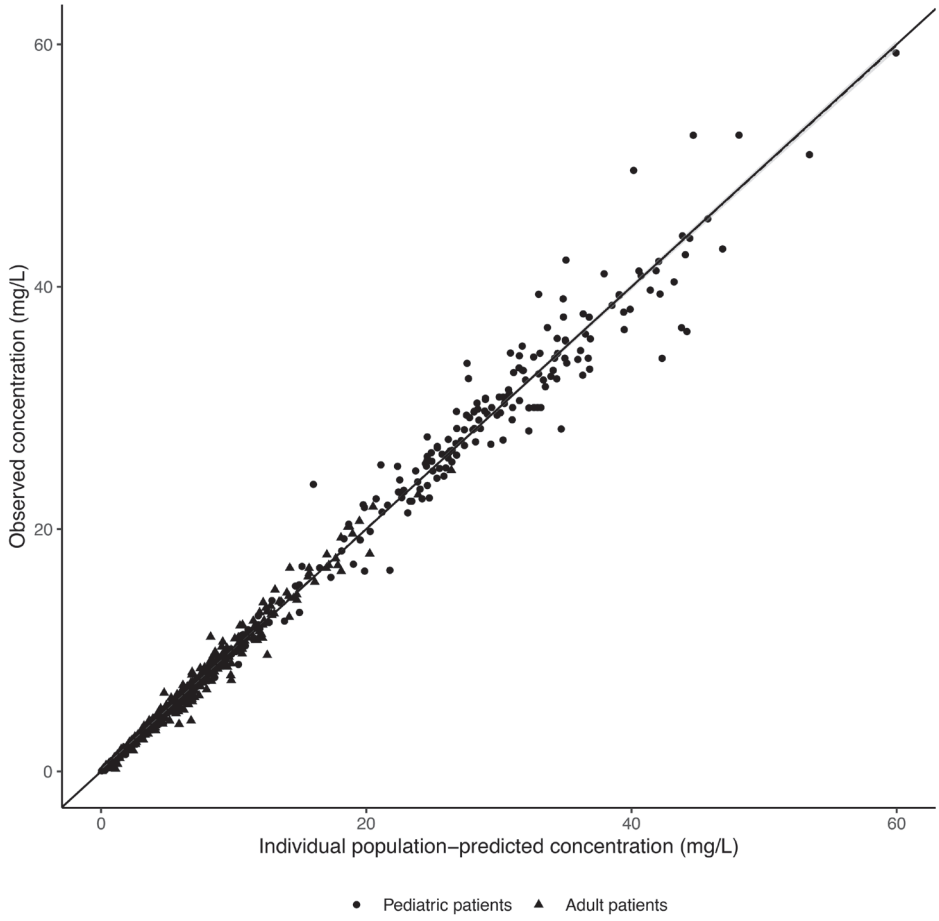

Figure S2B. Observed concentration versus individual-predicted concentration.
The black line indicates the line of unity and the dashed line indicates the trend of the observations.

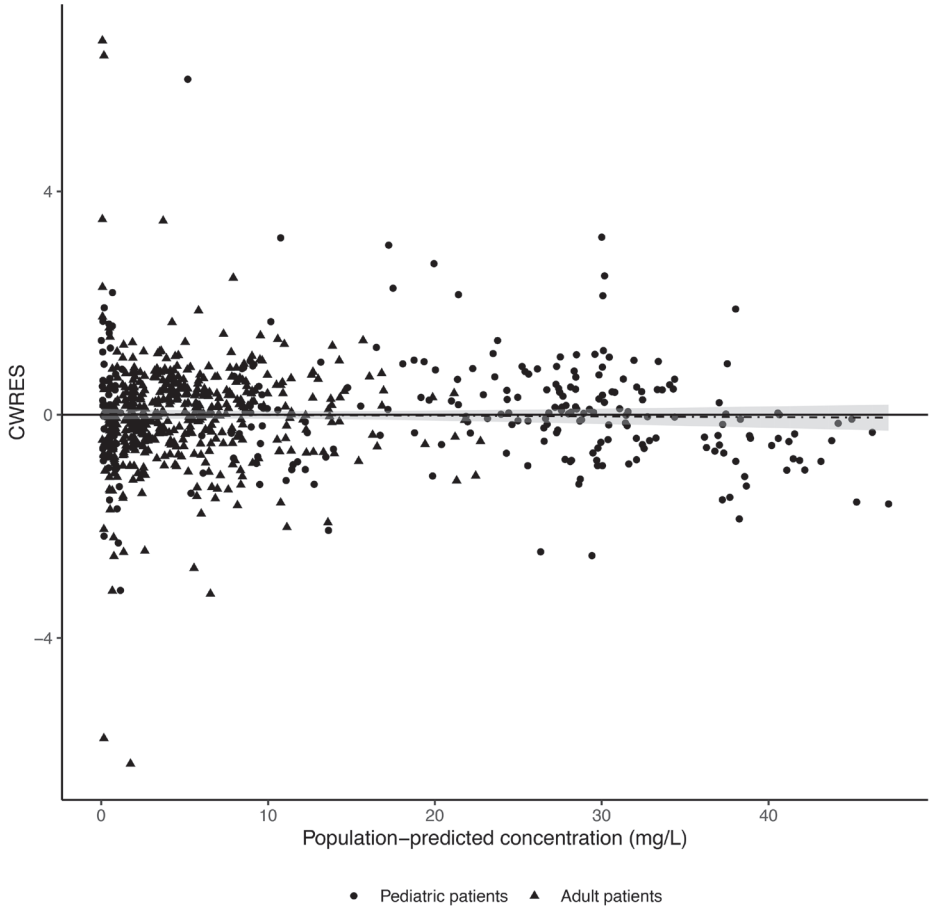

Figure S2C. Conditional weighted residuals versus population-predicted concentration.
The black line indicates the line of unity and the dashed line indicates the trend of the observations.

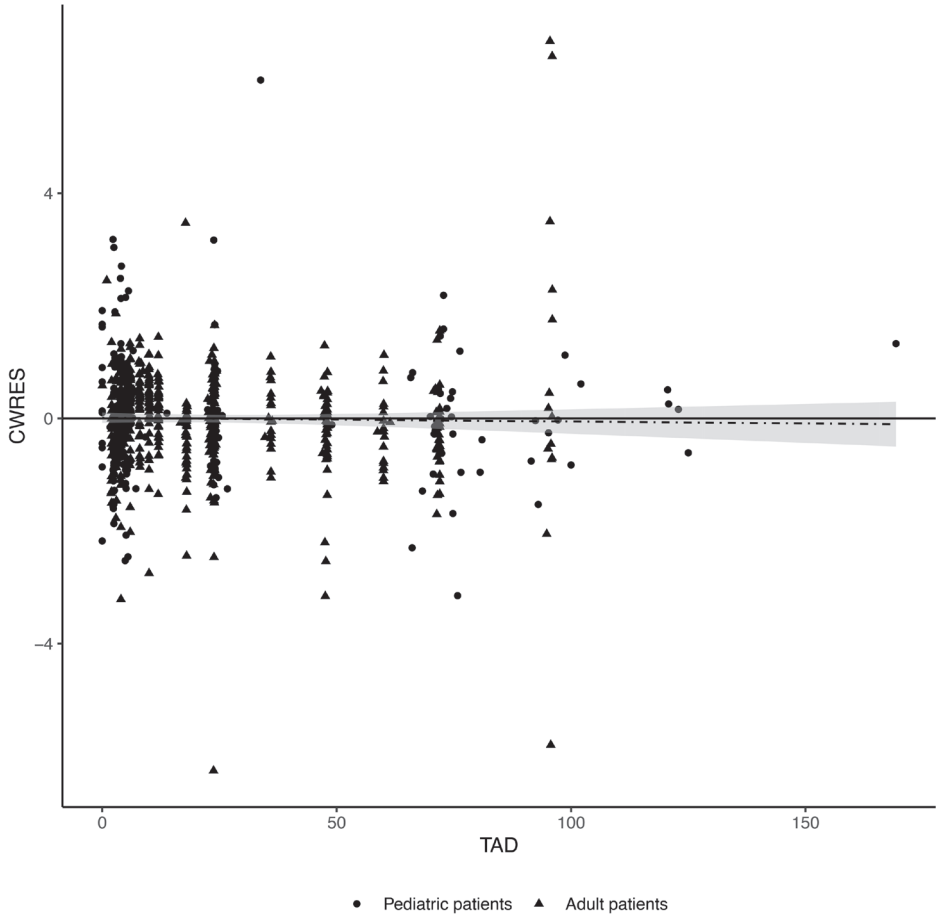

Figure S2D. Conditional weighted residuals versus time after dose (TAD).
The black line indicates the line of unity and the dashed line indicates the trend of the observations.

Visual predictive check

The prediction-corrected visual predictive checks for paediatric patients (A) and adult patients (B) are depicted in Figure 3 (panel A and B). The VPCs indicate that the predicted concentrations correspond well with the observed concentrations, as the percentiles lie mostly within the 95% confidence intervals.

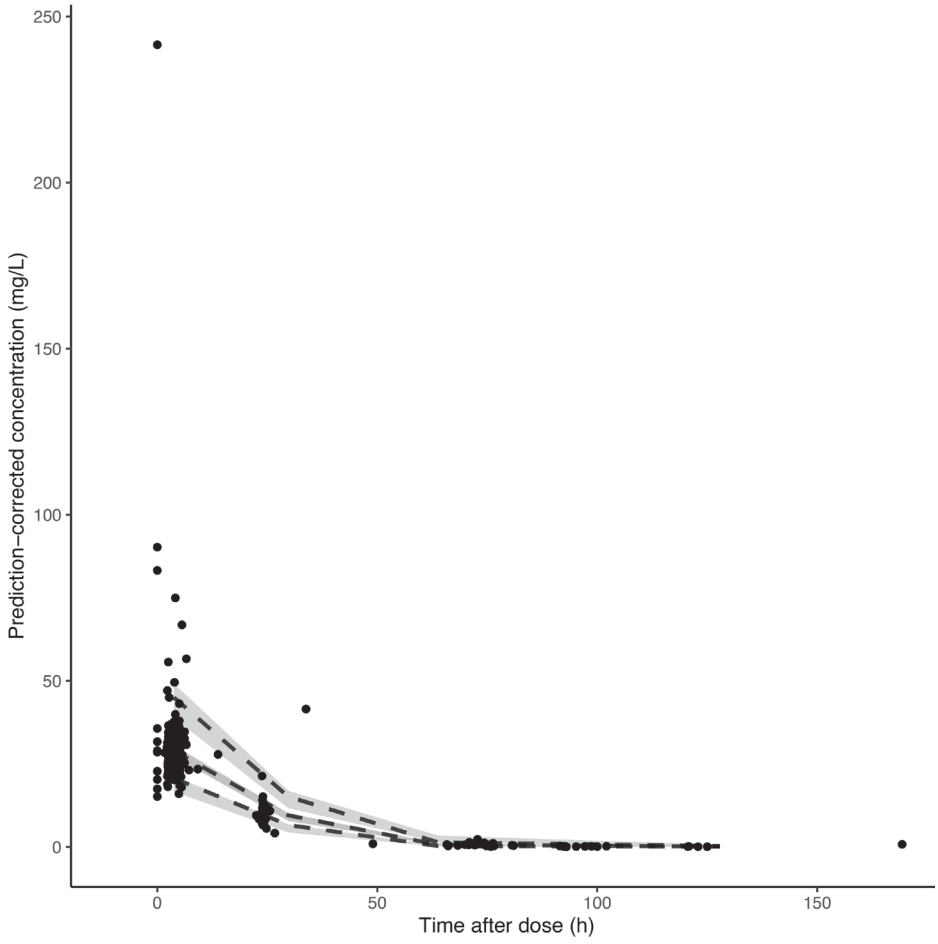

Figure S3A. Visual predictive check paediatric patients.

The black circles represent the observed concentrations. The dashed lines indicate the 5th, 50th and 95th percentile of the predicted concentrations. The shaded areas represent the 95% confidence intervals.

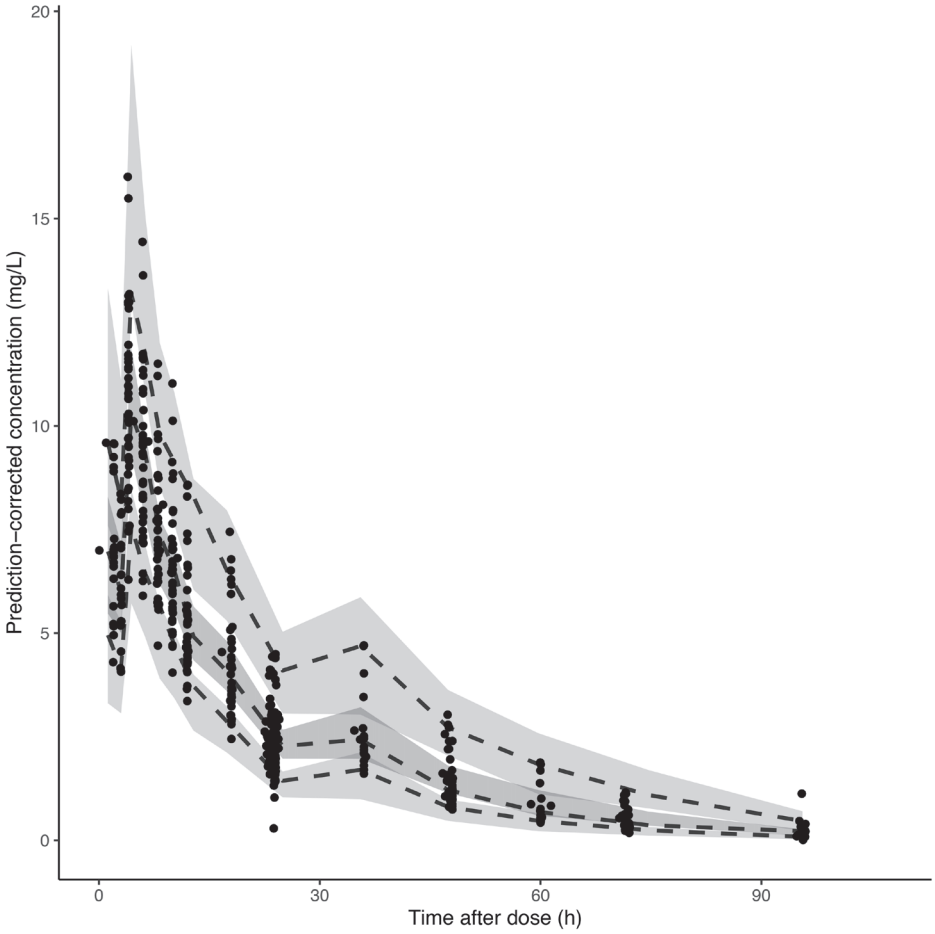

Figure S3B. Visual predictive check adult patients.

The black circles represent the observed concentrations. The dashed lines indicate the 5th, 50th and 95th percentile of the predicted concentrations. The shaded areas represent the 95% confidence intervals.

NONMEM control stream for final model

```
;;1. Based on: run052;
;;2. Description: CHECK 2-comp iv Cl & V separate ADULT&PED V1+V2 -CWRES DEFINITIEF;
;;x1. Author: user
;;3. Label:
$PROBLEM PK ANALYSIS OPTIMA
$INPUT C DROP ID AGE GEN WT HGT TIME EST AMT RATE DV MDV CMT EVID OCC
$DATA OPTIMA_MATADOR5.1.csv IGNORE=C
$SUBROUTINES ADVAN5
$MODEL
COMP=(CENTRAL)
COMP=(PERI1)
$PK
IF (NEWIND.LE.1) THEN
DOSE=0
TDOS=0
ENDIF
;Remember dose and time of dose
IF (AMT.GT.0) THEN
DOSE=AMT
TDOS=TIME
ENDIF
;Time after dose for every record
TAD=TIME-TDOS

;ADULT
ADULT=0
IF (ID.LT.21) ADULT=1

;FFM
FFM =
(1.11 + ((1-1.11)/((1+((AGE/7.1)**(1.1))))))*((9270*WT)/((8780+(244*(WT/((HGT*HGT)/10000))))))
IF(GEN.EQ.2) THEN
FFM =
(0.88 + ((1-0.88)/((1+((AGE/13.4)**(-12.7))))))*((9270*WT)/((6680+(216*(WT/((HGT*HGT)/10000))))))
ENDIF
; IOV
IF (OCC.EQ.1) IOV=ETA(1)
IF (OCC.EQ.2) IOV=ETA(2)
IF (OCC.EQ.3) IOV=ETA(3)
IF (OCC.EQ.4) IOV=ETA(4)
IF (OCC.EQ.5) IOV=ETA(5)
IF (OCC.EQ.6) IOV=ETA(6)
IF (OCC.EQ.7) IOV=ETA(7)
IF (OCC.EQ.8) IOV=ETA(8)
IF (OCC.EQ.9) IOV=ETA(9)
```

```
;ALLOMETRY SCALED TO 1.80M MAN OF 70 KG (FFM OF 57.18) & IOV
IF (ADULT.EQ.0) CL = THETA(1)*((FFM/57.19)**0.75) * EXP(ETA(10))*EXP(IOV)
IF (ADULT.EQ.1) CL = THETA(2)*((FFM/57.19)**0.75) * EXP(ETA(10))*EXP(IOV)
IF (ADULT.EQ.0) V1 = THETA(3)*((FFM/57.19)**1) * EXP(ETA(11))
IF (ADULT.EQ.1) V1 = THETA(4)*((FFM/57.19)**1) * EXP(ETA(11))
V2 = THETA(5)*((FFM/57.19)**1)
Q1 = THETA(6)*((FFM/57.19)**0.75) * EXP (ETA(12))
S1 = V1
K10=CL/V1
K12=Q1/V1
K21=Q1/V2

$ERROR
IPRED=F
IF (ADULT.EQ.0) Y=IPRED+(IPRED*(ERR(1)))
IF (ADULT.EQ.1) Y=IPRED+(IPRED*(ERR(2)))

$THETA
(0, 1)  ; 1 CL PED
(0, 2)  ; 2 CL ADULT
(0, 10) ; 3 V1 PED
(0, 15) ; 4 V1 ADULT
(0, 4) ; 5 V2
(0, 10)   ; 6 Q1
$OMEGA BLOCK(1) 0.01  ; 1 IOV
$OMEGA BLOCK(1) SAME ; 2 IOV
$OMEGA BLOCK(1) SAME ; 3 IOV
$OMEGA BLOCK(1) SAME ; 4 IOV
$OMEGA BLOCK(1) SAME ; 5 IOV
$OMEGA BLOCK(1) SAME ; 6 IOV
$OMEGA BLOCK(1) SAME ; 7 IOV
$OMEGA BLOCK(1) SAME ; 8 IOV
$OMEGA BLOCK(1) SAME ; 9 IOV
$OMEGA BLOCK(2)0.1  ; 10 IIV CL
0.05 0.1 ; 11 IIV V1
$OMEGA 0.2 ; 12 IIV Q
$SIGMA
0.02 ; PROP ERR PED
0.01 ; PROP ERR ADULT
$EST METHOD=1 INTER MAXEVAL=9999 NOABORT PRINT=1
$COV MATRIX=R PRINT=E; Xpose

$TABLE ID ADULT TIME TAD AMT AGE RATE DV MDV EVID IPRED CWRES NPDE WT PRED CL V1
V2 Q1 WT FFM ETA(10) ETA(11) ETA(12) ONEHEADER NOPRINT FILE=sdtabrun055.tab
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CHAPTER 6

MICAFUNGIN TWICE-A-WEEK FOR PROPHYLAXIS OF INVASIVE ASPERGILLUS INFECTIONS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA: A CONTROLLED COHORT STUDY

Didi Bury, Tom F.W. Wolfs, Eline W. Muilwijk, Marta Fiocco, Rob Pieters, Roger J. Brüggemann, Wim J.E. Tissing**

**equally contributed to this work*

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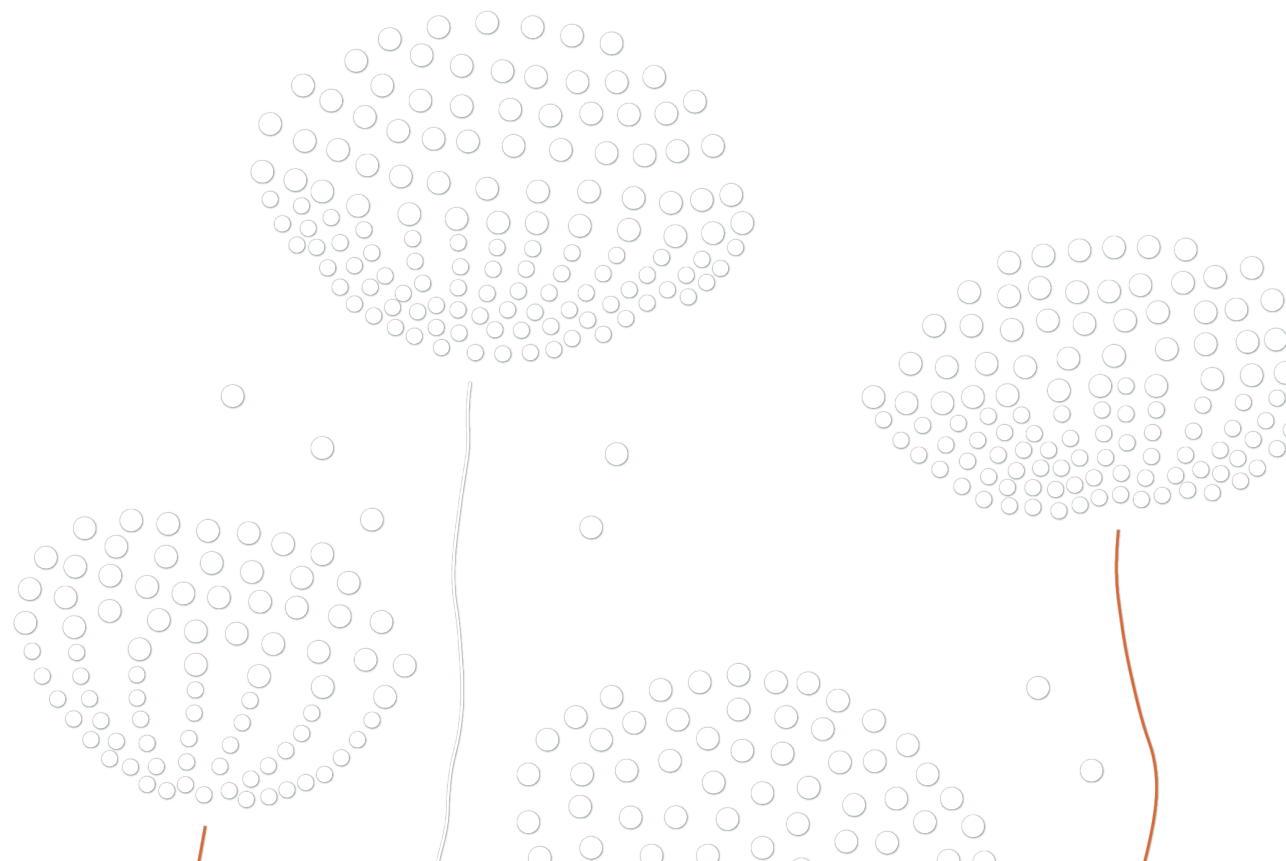

Abstract

Objectives

Invasive *Aspergillus* infections during the early phase of childhood acute lymphoblastic leukaemia (ALL) treatment come with morbidity and mortality. The interaction with vincristine hampers first-line azole prophylaxis. We describe the efficacy of an alternative twice-a-week micafungin regimen for *Aspergillus* prophylaxis.

Methods

Newly diagnosed paediatric patients with ALL treated according to the ALL-11 protocol received micafungin twice-a-week (9 mg/kg/dose [max. 300 mg]) during the induction course (first 35 days of treatment) as part of routine care. A historical control cohort without *Aspergillus* prophylaxis was used. During the first consolidation course (day 36-79), standard itraconazole prophylaxis was used in both groups. The percentage of proven/probable *Aspergillus* infections during the induction/first consolidation course was compared between the cohorts. The cumulative incidence of proven/probable *Aspergillus* infections was estimated using a competing risk model. For safety evaluation, liver laboratory chemistry values were analysed.

Results

A total of 169 and 643 paediatric patients with ALL were treated in the micafungin cohort (median age: 4 years [range 1-17]) and historical cohort (median age: 5 years [range 1-17]). The percentage of proven/probable *Aspergillus* infections was 1·2% (2/169) in the micafungin cohort versus 5·8% (37/643) in the historical cohort (p=0.012; Fisher's exact test). The differences in estimated cumulative incidence were assessed (p=0·014; Gray's test). Although significantly higher ALT/AST values were reported in the micafungin cohort, no clinically relevant side effects were observed.

Conclusions

Twice-a-week micafungin prophylaxis during the induction course significantly reduced the occurrence of proven/probable *Aspergillus* infections in the early phase of childhood ALL treatment.

Introduction

The 5-year overall survival of childhood acute lymphoblastic leukaemia (ALL) has increased to ~90%.[1] To further improve overall survival, reducing treatment-related mortality (TRM) remains an important focus of interest. One of the leading causes of TRM in paediatric patients with haematological malignancies is invasive fungal disease (IFD)[2], most importantly *Aspergillus* infections. Two recent guidelines for paediatric haematology patients recommend considering antifungal prophylaxis during at-risk treatment courses of ALL treatment.[3, 4] The majority of IFD occur during the induction and first consolidation course, when paediatric patients with ALL are severely immunocompromised.[5] *Aspergillus* spp. are most frequently responsible for fungal infections in this phase, with an incidence of ~6% [data on file, Dutch Childhood Oncology Group (DCOG)] for invasive *Aspergillus* infections. This high incidence has prompted the use of *Aspergillus* prophylaxis during the early treatment phase of childhood ALL.

Finding a suitable antifungal agent for *Aspergillus* prophylaxis remains challenging during the induction course (first 35 days of treatment) of ALL treatment. The required antifungal agent needs to be compatible with the chemotherapeutic agents given, and must fit a patient-friendly dosing schedule during this mostly outpatient treatment phase. Triazoles are the preferred agents for primary prophylaxis in patients with a high risk to develop IFD.[4] Considering the clinically relevant drug-drug interaction of triazoles with vincristine[6], these agents do not meet the specific profile for a prophylactic agent outlined above. In the past years, echinocandin prophylaxis in a daily regimen has been demonstrated to be of value in paediatric patients with acute myeloid leukaemia (AML) in a large controlled trial but with varying outcomes in other smaller studies for *Aspergillus* prophylaxis in paediatric haematology populations.[7] The proven efficacy of echinocandins for prophylaxis of invasive *Aspergillus* infections in patients with AML[7], offers an alternative perspective for *Aspergillus* prophylaxis in the early setting of ALL treatment. Echinocandins are generally well tolerated due to their fungi-specific target and no clinically relevant drug-drug interactions are expected.[8] The difficulty is their invasive daily intravenous dosing regimen.

An intermittent twice-a-week echinocandin dosing regimen may be a more patient-friendly approach for this outpatient treatment phase. The pharmacokinetic background of such intermittent regimens has been reported in adult patients for both anidulafungin and micafungin.[9, 10] We recently showed that a twice-a-week micafungin regimen in paediatric patients was pharmacokinetically equivalent to a daily micafungin regimen in adult patients.[11] This paper describes the efficacy of this twice-a-week micafungin regimen for prophylaxis of invasive *Aspergillus* infections in the early phase of childhood ALL treatment.

Methods

Study design and patients

The set-up of this investigation was a prospective, observational treatment protocol with a historical control group.

All newly diagnosed paediatric patients with ALL between 2018 and 2020 in the Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands, aged between ≥1 and <18 years and treated according to the DCOG ALL-11 protocol were included in the prospective cohort. They received micafungin in a twice-a-week regimen during the induction course (first 35 days of treatment) as part of standard care.

The historical control cohort consisted of newly diagnosed paediatric patients with ALL between 2012 and 2018, aged between ≥1 and <18 years and treated according to the same DCOG ALL-11 protocol. These patients did not receive antifungal prophylaxis during the induction course, as this was not part of standard practice during this time period.

Both the micafungin and the historical cohort received standard itraconazole prophylaxis during the first consolidation course (days 36-79 of treatment). An overview of the induction and first consolidation course (first 79 days of treatment) of the DCOG ALL-11 protocol and prophylactic antifungal strategy is given in Figure 1.

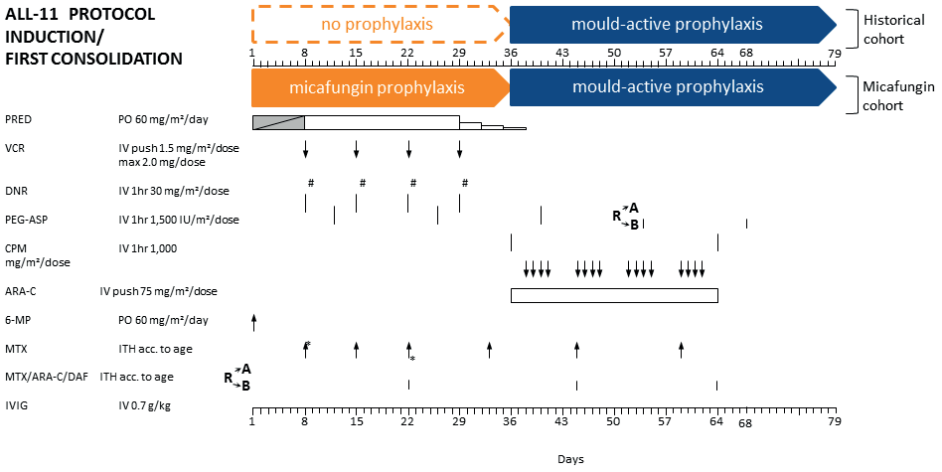

Figure 1. An overview of the induction and first consolidation course of ALL treatment with a different antifungal prophylaxis strategy in the micafungin and historical cohort.

Abbreviations: PRED=prednisolone; VCR=vincristine; DNR=daunorubicine; PEG-ASP=PEG-asparaginase; CPM=cyclophosphamide; ARA-C= Cytosine Arabinoside; 6-MP=6-mercaptopurine; MTX= methotrexate; DAF= Diadreson F aquosum; IVIG= intravenous immunoglobulines. #Not in children with Down Syndrome. *Only in children with central nervous system involvement or traumatic puncture with leukemic cells at diagnosis.

Ethics

All patients provided written informed consent for the DCOG ALL-11 protocol. The study protocol was approved by the Medical Ethics Committee Erasmus MC of Rotterdam (MEC-2018-1684).

Procedures

As of 2018, paediatric patients with ALL received off-label micafungin in a twice-a-week regimen during the induction course as mould-active prophylaxis. Micafungin was given twice-a-week in a dose of 9 mg/kg/administration (max. 300 mg) over a central venous line, with an infusion time of 2 hours per dose. The dose was chosen based on a bio-equivalence approach, where the cumulative licensed weekly dose of 2-4 mg/kg/day was given in two administrations. Details on this dosing strategy have recently been published.[11]

During the first consolidation course both the micafungin and historical cohort received itraconazole prophylaxis according to the standard DCOG ALL-11 protocol. In case of intolerance for itraconazole, switching *Aspergillus* prophylaxis was decided by the treating physician.

The toxicity adverse events (AEs) were documented and evaluated by data managers of the DCOG according to the standard ALL-11 protocol procedures. During the induction course laboratory values of blood bilirubin, alanine transaminase (ALT) and aspartate transaminase (AST) were routinely monitored before every PEG-asparaginase infusion every two weeks. The highest measured laboratory value during the induction course was used for categorizing toxicity AEs according to the Common Terminology Criteria for Adverse Events (CTCAE) grading scale (Version 4.03[12]). The categorization of the toxicity AEs was as follows: for blood bilirubin; no or low grade, >3.0 - 10.0 times upper limit of normal (ULN), >10.0 times ULN or unknown, and for both AST and ALT; no or low grade, >5.0 - 20.0 times ULN, >20.0 times ULN or unknown. In addition, the electronic health care system was checked for spontaneous reported micafungin infusion-related AEs documented by nurses.

Definitions

Proven and probable *Aspergillus* infections were defined according to the European Organization for Research and Treatment in Cancer/Mycoses Study Group 2008 (EORTC/MSG) criteria.[13] Categorizing fungal infections according to the EORTC/MSG criteria was performed independently by two researchers of our group (DB and TW).

Outcomes

The primary outcome of interest was the percentage of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course (i.e. the first 79 days of treatment) of the DCOG ALL-11 protocol in the micafungin and the historical control cohort.

The secondary outcomes included I) the cumulative incidence of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course, and II) toxicity AEs of the twice-a-week micafungin regimen during the induction course.

Statistical analyses

For the sample size computations information about the percentage of invasive *Aspergillus* infections in the historical and micafungin cohorts was used. The percentage during the induction and first consolidation course was equal to 6% in the historical cohort and was assumed to be 1% in the micafungin cohort. A group sample size of 178 micafungin-treated patients and 600 patients in the historical cohort achieved 80% power to detect a difference between the two groups of 5%. The test statistics used is the two-sided Z-test with continuity correction and pooled variance. The significance level was 5%.

The efficacy of micafungin was evaluated on an intention-to-treat basis. The difference between the percentage of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course in the micafungin and historical cohort was assessed by using the same test as discussed in the sample size computations.

A competing risk model [14] from start of treatment was used to estimate the cumulative incidence (i.e. the cumulative failure rates over time due to a particular cause) of proven or probable invasive *Aspergillus* infection during the induction and first consolidation course. Patients alive without having experienced any event at the end of the study period were censored.

Four competing events were included in the model: I) proven or probable *Aspergillus* infection during the induction and first consolidation course, II) use of any mould-active agent for treatment of an IFD other than a proven or probable *Aspergillus* infection during the induction course, III) major violation of the DCOG ALL-11 protocol during both the induction and first consolidation course, and IV) all-cause mortality during both the induction and first consolidation course. The Gray's test was used to assess the difference between the cumulative incidence of proven and probable invasive *Aspergillus* infections in the two cohorts.[14]

Fisher's exact test was used to assess the difference between different degrees of toxicity in the two cohorts.

Statistical analyses were mainly performed in R software environment with the library mstate and cmprsk[15-17], the toxicity analysis was performed using SPSS software (version 26.0.0.1.).

Results

Patient characteristics

A total of 169 and 643 paediatric patients were included in the micafungin and historical cohort, respectively. The patient characteristics of both cohorts are depicted in Table 1. The cohorts were comparable concerning age, gender, immunophenotype of ALL, genetic variation of ALL, ALL treatment response and duration of the induction course. During the induction course, the mean number of micafungin doses applied was 9 (range 5-14).

Table 1. Patient characteristics

	Historical cohort	**Micafungin cohort**
Total number of patients *N*	643	169
Age; median (range) in years	5·0 (1-17)	4·0 (1-17)
Gender *N(%)*		
Female	260 (40·4%)	73 (43·2%)
Male	383 (59·6%)	96 (56·8%)
Immunophenotype *N(%)*		
Pro-B ALL	12 (1·9%)	3 (1·8%)
c-ALL	373 (58·0%)	102 (60·4%)
Pre-B ALL	166 (25·8%)	43 (25·4%)
T-ALL	92 (14·3%)	21 (12·4%)
Genetic variation *N(%)*		
t(11;v) or MLL-rearrangement	12 (1·9%)	5 (3·0%)
t(4;11) or MLL-AF4	6 (0·9%)	2 (1·2%)
t(12;21) or TEL-AML1	142 (22·1%)	41 (24·3%)
t(1;19) or E2A-PBX1	16 (2·5%)	7 (4·1%)
del(IKZF1)	74 (11·5%)	19 (11·2%)
Down's syndrome	17 (2·6%)	5 (3·0%)
Treatment response *N(%)*		
Good prednisolone response (day 8)	581 (90·4%)	150 (88·8%)
Complete remission (day 33)	614 (95·5%)	158 (93·5%)
Duration treatment course		
Induction course; mean duration (range) in weeks	5·0 (2-33)	5.0 (4-11)

Abbreviations: ALL = acute lymphoblastic leukaemia; pro-B ALL = precursor B acute lymphoblastic leukaemia with no expression of CD10; c-ALL = common acute lymphoblastic leukaemia; Pre-B ALL = precursor B-lineage acute lymphoblastic leukaemia; T-ALL= T-lineage acute lymphoblastic leukaemia.

Outcomes

In the micafungin cohort 2/169 (1·2%) patients were diagnosed with a probable *Aspergillus* infection compared to 37/643 (5·8%) patients with proven and probable *Aspergillus* infections in the historical cohort (p=0.012; test for two proportions with continuity correction). With the number of patients present in our study, we were able to detect a 5% difference with a power equal to 78.34%. The two probable *Aspergillus* infections in the micafungin cohort occurred during the consolidation course. In the historical cohort, 13 proven and 24 probable *Aspergillus* infections were identified, of which 19 occurred during the induction course and 18 during the consolidation course.

The cumulative incidence of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course is depicted in Figure 2; (p=0·014 based on the Gray's test).

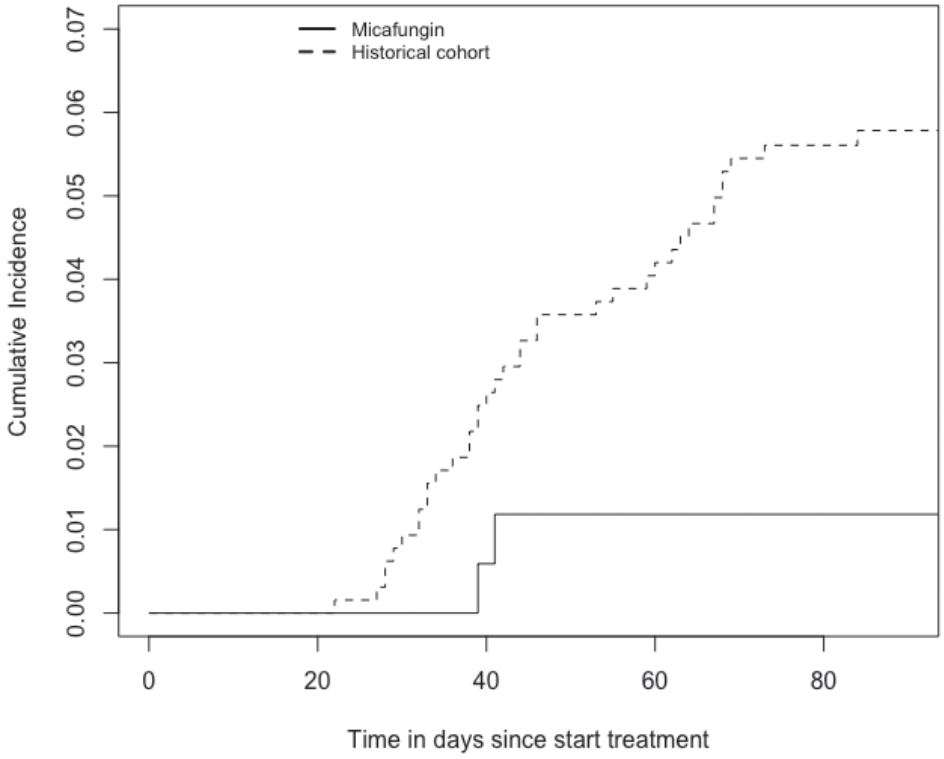

Figure 2. Cumulative incidence of invasive Aspergillus infections.

The cumulative incidence function of invasive *Aspergillus* infections in the micafungin (solid line) and historical cohort (dashed line) during the induction and first consolidation course of ALL treatment.

An overview of the toxicity AEs, including blood bilirubin, ALT and AST during the induction course for both cohorts is given in Table S1 (Supplementary file). Both ALT and AST values were significantly increased in the micafungin cohort compared to the historical cohort during the induction course, but bilirubin levels were not significantly different. In 9/169 (5.3%) patients micafungin prophylaxis was temporarily stopped (n=4; all of whom reinitiated micafungin prophylaxis successfully) or early terminated (n=5) due to elevated liver values. In one of these patients chemotherapy was delayed for four days due to elevated liver values including AST, ALT, and bilirubin.

In 2/169 (1.1%) paediatric patients an infusion-related AE was reported in the electronic health care system. These infusion-related AEs included I) red cheeks during infusion, and II) red hand palms and blue fingertips during infusion. In both patients these were transient infusion-related AEs. The infusion-related AEs were managed by I) pausing micafungin infusion for half an hour and restarting the infusion without signs of infusion-related problems, and II) terminating micafungin infusion during the induction protocol. In the last patient, micafungin infusion was restarted during the first consolidation course due to difficulties with itraconazole intake and infusion-related problems were no longer observed.

Discussion

In this report we showed that a twice-a-week prophylactic micafungin regimen resulted in a significantly lower occurrence of invasive *Aspergillus* infections during the induction course of ALL treatment in paediatric patients without clinically relevant side effects.

This accords with the previously demonstrated efficacy of a daily caspofungin regimen for prophylaxis of invasive *Aspergillus* infections in paediatric patients with acute myeloid leukaemia showing a decreased cumulative incidence of proven and probable *Aspergillus* infections as compared to a daily fluconazole regimen.[7] Although they studied a different patient population with another risk-profile, antifungal agent and follow-up period, they also demonstrated the efficacy of an echinocandin regimen for prophylaxis of invasive *Aspergillus* infections. Furthermore, our results are in line with two other, small (n=9 and n=21) studies on alternative micafungin dosing regimens of twice-a-week 5 mg/kg with a simulated target attainment, and a twice-a-week 3-4 mg/kg with clinical observations in both *Candida* and *Aspergillus* prophylaxis.[18, 19] Our clinical study showed that a less invasive twice-a-week regimen is possible without compromising its efficacy. This patient-friendly regimen is of importance, as ALL treatment is mostly outpatient.

The main limitation of this study is its design. A randomized controlled trial would have been optimal. First of all, we felt the clinical urge to start a prophylactic regimen given the high incidence in the historical cohort (~6%). Secondly, given the benefits of this historical cohort, such as the large number of paediatric patients and the exact similar ALL treatment protocol in both cohorts, this seemed a suitable control group. Lastly, this study was part of the DCOG ALL-11 study, a prospective study for the treatment of childhood ALL, with an already existing database on treatment effect and toxicity. A note of caution is required in the interpretation of the results as the study technically did not meet the power (78.34% versus 80%) due to the opening of the ALLTogether protocol in July 2020.

To minimize the risk of bias in the reported *Aspergillus* infections, the fungal infections documented by the DCOG were checked and categorized for both cohorts according to the EORTC/MSG independently by two researchers.[13] In the unlikely event that the documentation of *Aspergillus* infections was incomplete in the historical cohort, the decrease in the occurrence of these infections using the twice-a-week micafungin strategy would be even more pronounced. Compared to the historical cohort, the occurrence of *Aspergillus* infections during the first consolidation course, when all patients received *Aspergillus* prophylaxis, was also lower. We could hypothesize that given the onset of *Aspergillus* infections over time, most infections were prevented during the first consolidation course due to micafungin prophylaxis in the induction course.

For the safety of micafungin, it was decided to focus on laboratory chemistry values as these were routinely reported and structured nurse- or physician-directed reporting of AEs was not part of clinical practice. It is not expected that clinically relevant toxicity of micafungin was overseen, given the close monitoring of these patients in clinical care. We demonstrated that this twice-a-week micafungin dose was generally well tolerated. Although increased AST and ALT values were reported during the induction course in the micafungin cohort, these elevated values were not considered clinically relevant in the vast majority of the patients. The comparable bilirubin values and duration of the induction course between the micafungin and historical cohort strengthens the assumption that micafungin did not lead to clinically relevant toxicity.

A dose reduction was advised in 19 out of 47 patients. This was included in our strategy in the initial phase of the study as a precautionary measure to prevent toxicity despite the higher tolerable dose known from literature. The trigger for dose reduction was based on an empirically chosen measure of exposure of micafungin together with a clinical judgment of both the pharmacist and treating physician to prevent unknown side effects.

As no clinically relevant micafungin toxicity occurred during this initial phase, the decision was made to continue with a 9 mg/kg (max. 300 mg) micafungin dose to all patients in the clinical evaluation part. Nevertheless, it would be interesting to address whether lower dosage micafungin regimens would result in comparable efficacy for *Aspergillus* prophylaxis, specifically if they would come at the benefit of lower liver enzymes. As toxicity in our case was very mild, the need to study this matter promptly is less urgent.

To conclude, a twice-a-week micafungin regimen during the induction course of childhood ALL treatment resulted in a significantly lower percentage of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course compared to the historical cohort without antifungal prophylaxis during the induction course. When a high incidence in local epidemiology drives the need for *Aspergillus* prophylaxis, a patient-friendly twice-a-week micafungin regimen could be used for prophylaxis of invasive *Aspergillus* infections during the early phase of childhood ALL treatment.

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Author contribution statement

Design of the protocol: DB, WT, TW, RP and RB. Data collection: DB. Interpretation of the data: DB, WT, TW, and RB. Formal statistical analysis: DB, MF. Writing original draft: DB, WT, TW, MF and RB. Critical revision draft: EM, RP. Editing draft: DB, WT, TW, MF and RB. All authors provided approval of the final version.

Transparency declarations

No conflicts of interest/competing interests are applicable for this work.

Disclosures outside of this work: R.J.B. has served as a consultant to Astellas Pharma, Inc., F2G, Amplyx, Scynexis, Gilead Sciences, Mundipharma, and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, and Pfizer, Inc. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. None of the other authors have a conflict to declare.

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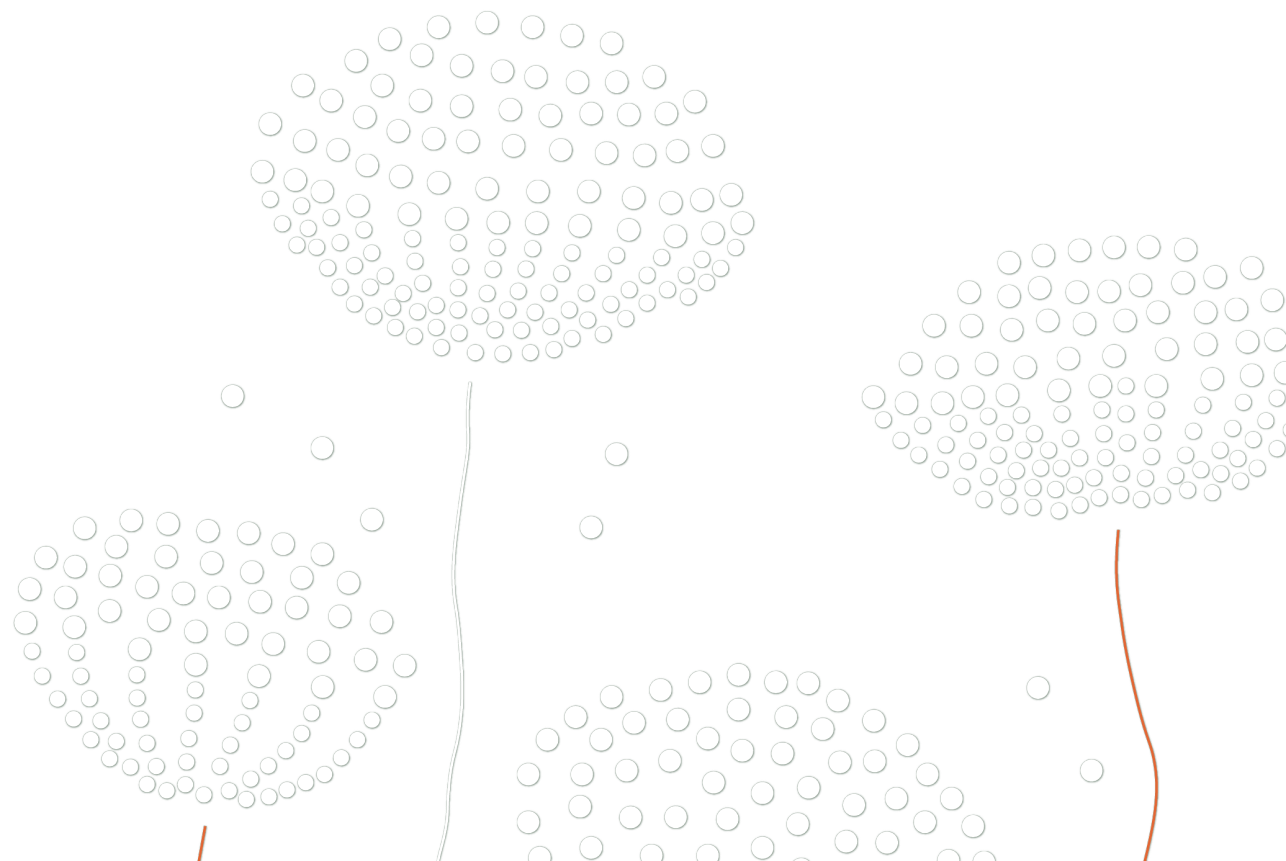
CHAPTER 7

SUMMARY AND GENERAL DISCUSSION



Invasive mould disease (IMD) is a life-threatening infection with a high morbidity and mortality rate in immunocompromised and hospitalized paediatric patients, especially in patients with haematological malignancies. The overall aim of this research project was to develop and/or optimize mould-active dosing strategies for the prophylaxis and treatment of IMD in paediatric cancer patients.

Therefore, the topics were addressed in three major sections. In section I of this thesis the clinical presentation and outcome of IMD in paediatric patients with acute lymphoblastic leukaemia (ALL) are described (**Chapter 2**). In section II of this thesis the pharmacokinetics of different mould-active agents in paediatric patients are examined (**Chapter 3, 4 and 5**). In section III of this thesis the efficacy of micafungin for prophylaxis of invasive *Aspergillus* infections in an alternative dosing regimen is evaluated (**Chapter 6**).

This concluding chapter summarizes the main findings of this thesis, followed by the strengths and limitations, implications for clinical practice, future perspectives and a general conclusion.

In **Chapter 2** the epidemiology, clinical presentation, treatment and outcome of IMD in paediatric patients (1-18 years of age) with acute lymphoblastic leukaemia are described from 2012-2018. In total, 643 patients were included in this study. The incidence rate of probable and proven IMD was 7.3% during the induction and first consolidation course of ALL treatment. Aspergillosis was diagnosed in 89.4% of the patients, followed by mucormycosis in 6.4% and alternariosis in 4.2% of the patients. Our data suggests that paediatric patients with IMD tend to be older (14 years [IQR 7-16]) than those who do not develop IMD (5 years [IQR 3-10]). As serum galactomannan was the trigger for diagnostic workup in only 11% of the episodes, the diagnostic value of galactomannan screening could be discussed. Specifically during courses were mould-active prophylaxis is administered. The most prevalent clinical symptoms at presentation included persistent fever and respiratory symptoms. The lungs were the most common site of infection in 94% of the patients. CNS involvement was remarkably high and was diagnosed in 34% of the patients. Half of the patients with CNS involvement were asymptomatic at the time of diagnosis. The initial combination therapy of liposomal amphotericin B and voriconazole seems to be justified given the azole resistance frequency for *Aspergillus* isolates of 21% in our paediatric cohort. The 6-week mortality rate after IMD diagnosis was 10.6%, and the 12-week mortality rate was 14.9%. The abovementioned findings highlight the importance of effective prophylactic strategies and warrant early brain imaging in children even in the absence of neurological symptoms.

An up-to-date review of the literature on pharmacokinetic data of triazoles in paediatric patient populations is provided in **Chapter 3**. This review shows that the pharmacokinetics of fluconazole are extensively studied in the neonatal population and the pharmacokinetics of voriconazole are extensively studied in children and adolescents. In contrast, isavuconazole, itraconazole and posaconazole are studied to a limited extend. Fluconazole data in children and adolescents are understated, while for other triazoles the pharmacokinetics data in neonates and infants urgently need to be studied. Future studies should explore the pharmacokinetics of the newest triazole agents and understanding the bioavailability of the available formulations. Furthermore, more information is needed about interactions with food or administration over a nasogastric tube, the effect of CYP genotypes and other metabolic routes. Other factors that should be taken into account are the unbound drug concentrations for highly protein bound agents and the development and pharmacokinetics of new oral formulations that can easily be deployed in paediatric patients. In addition, information on the pharmacokinetics of triazoles in critically ill patient populations, the impact of dialysis, ECMO as well as renal or hepatic impairment is lacking in most cases and should warrant further exploration. Better understanding of the pharmacokinetics is necessary for optimal clinical care and remaining knowledge gaps will need to be clarified.

The pharmacokinetics of isavuconazole in Dutch paediatric cancer patients is examined in **Chapter 4**. This study indicated a reduced isavuconazole bioavailability of 41% after administration of opened capsules via a nasogastric tube. Instead, clinicians should consider administration of the reconstituted injection formulation over a nasogastric tube, which demonstrated bioequivalence compared to orally administered isavuconazole in a study by Desai et al.[1], in combination with Therapeutic Drug Monitoring. Furthermore, total and unbound (pharmacologically active) isavuconazole pharmacokinetics were reported with a five-fold range in the unbound fraction. Currently, total isavuconazole concentrations are measured for the purpose of Therapeutic Drug Monitoring. In case the unbound fraction varies widely, total concentrations may not accurately represent the pharmacologically active concentrations of isavuconazole. Therefore, we proposed utilizing unbound isavuconazole drug concentrations for therapeutic drug monitoring and for defining target concentrations associated with efficacy and toxicity.

In **Chapter 5** the pharmacokinetics of a twice-a-week micafungin regimen in Dutch paediatric patients with ALL are explored. The pharmacokinetic data obtained from this large paediatric (n=61) cohort were combined with an adult (n=20) cohort and supports the rationale of a micafungin twice-a-week regimen. Our analysis proved that

a micafungin twice-a-week regimen is at least pharmacokinetically equivalent to a daily regimen. The predicted exposures (AUC_{0-168}) for the 5 mg/kg, 7 mg/kg, 9 mg/kg and flat dosing per weight band regimens exceeded the adult reference exposure. The greater micafungin exposures seem to be caused by a slower than anticipated clearance in our paediatric leukemic patients.

We evaluated the efficacy of this twice-a-week micafungin regimen for *Aspergillus* prophylaxis in Dutch paediatric patients with ALL in **Chapter 6**. A twice-a-week micafungin regimen during the induction course of childhood ALL treatment resulted in a significantly lower percentage of proven and probable invasive *Aspergillus* infections during the induction and first consolidation course in the micafungin cohort (1.2%; n=169) compared to the historical cohort (5.8%; n=643) without mould-active prophylaxis during the induction course. Furthermore, we demonstrated that this twice-a-week micafungin dose was generally well tolerated. When a high incidence in local epidemiology drives the need for *Aspergillus* prophylaxis, a patient-friendly twice-a-week micafungin regimen could be used for prophylaxis of invasive *Aspergillus* infections during the early phase of childhood ALL treatment.

In this thesis, an overview of invasive mould disease in paediatric patients with ALL has been given. We tried to cover the whole spectrum of invasive mould disease, from the epidemiology in our paediatric population to the pharmacokinetics of new mould-active agents and regimens and the efficacy of new prophylactic and treatment approaches.

Translation of findings into clinical practice

Some findings of our study were directly translated into clinical practice. In **Chapter 2**, it was concluded that there is a need for suitable mould-active prophylaxis during the induction course of ALL treatment, ensuring safe use with vincristine. The twice-a-week micafungin regimen, that has been evaluated in **Chapters 5 and 6**, has now been implemented in the current ALLTogether treatment protocol during the induction course of childhood ALL treatment in the Netherlands. In **Chapter 2**, combination therapy was found to be necessary due to the high *azole* resistance frequency, and early brain imaging seemed important given the high number of CNS involvement. Based on these conclusions, initial combination therapy and early brain imaging remained part of the standardized protocol in the Netherlands. The use of serum galactomannan screening was put up for further discussion. Additional data regarding serum galactomannan results have recently been collected, and in line with the (inter)national guidelines serum galactomannan screening was stopped for paediatric patients with ALL on mould-

active prophylaxis, in December 2023 in The Netherlands.[2, 3] Detailed radiology findings in paediatric patients remain an important topic for future research and are currently investigated by our research group. In our review in **Chapter 3** we defined research gaps. Since the time we reviewed the literature some of these gaps have been studied or are currently being studied by (other) research groups, such as the optimized fluconazole therapy in preterm infants.[4] Fluconazole pharmacokinetics in children and adolescents are currently being studied. Furthermore, the pharmacokinetic and pharmacodynamics of posaconazole have been extensively described.[5] Lastly, the pharmacokinetic data from **Chapter 4**, was used in the application to obtain the "add on" status of isavuconazole in paediatric patients. The five-fold range in unbound fraction of isavuconazole, as found in this chapter, was in contrast to adult data, but in line with the results from a published report with critically ill patients.[6] In addition, a call to reconsider pharmacokinetic and pharmacodynamic targets and breakpoints of isavuconazole given the high variability in unbound fractions has recently been published.[7] Furthermore, isavuconazole pharmacokinetics in paediatric cancer patients are currently further evaluated in the Princess Máxima Center.

Future perspectives

From all the research conducted, I want to discuss two topics that have the highest priority for future research. One topic is on pharmacokinetic investigations and the second topic is on the design and setup of a combined dose finding and clinical study. In the next paragraphs, each topic will be separately discussed.

Pharmacokinetic investigations needed in paediatric patients with ALL.

I recommend to perform oral absorption studies for drugs after administration over a nasogastric tube, as a significant number paediatric haemato-oncology patients receive their medication via this route. Interestingly, in **Chapter 4**, we found a significantly decreased bioavailability of isavuconazole after administration of the opened oral capsules over a nasogastric tube. This study was intended to explore the exposure of isavuconazole, and the pharmacokinetic sampling scheme was therefore centered on assessing isavuconazole clearance. Despite the non-optimal design for determining oral bioavailability, the differences in absorption were significant, which shows that the absorption of isavuconazole when given over the nasogastric tube is diminished. Various reasons for this erratic bioavailability have been discussed in chapter 4. But the consequences of these findings extend beyond the use of isavuconazole. I believe that prior to deployment of any drugs in the clinical setting for paediatric haemato-oncology

patients, assessment of the bioavailability when given over the nasogastric tube should have been conducted and clear guidance should be available on the optimal use these new drugs via a tube. Currently, there are several new mould-active agents in the pipeline that are available as oral formulation. Olorofim in the class of orotomides, ibrexafungerp in the class of triterpenoides, and fosmanogepix in the class of 'gepix'.[8] When investigating these drugs, various factors should be addressed. First of all, the stability of the formulation should be assessed, including the stability after opening capules, crushing of tablets or when using the intravenous formulation for administration over a tube. Furthermore, a sampling scheme appropriate for capturing the absorption phase would be needed to address potential differences in bioavailability. While a multiple-dosing schedule provides generally a more comprehensive assessment of a drug, including information regarding the steady-state conditions and accumulation over time [9], this is also a quite invasive schedule for patients. For addressing bioavailability after administration via a tube, I believe a single dose study could be performed. It not only provides the basic pharmacokinetic data needed to define differences in bioavailability, but also reduces the burden for the patients. Ideally, the bioavailability would be studied in an oral regimen and in a regimen after administration over a tube, in comparison to an intravenous regimen. Given that the majority of patients receive their medication over a tube, it would be advisable to at least include a control group that receives the intravenous formulation of the drug to determine the absolute bioavailability. Furthermore, it would be important to consider the interaction with (different types of) enteral feeding.[10]

Reflections on combined pharmacokinetics and clinical efficacy investigations

In **Chapter 5 and 6**, we studied the pharmacokinetics within the efficacy evaluation study of a twice-a-week micafungin regimen. However, to study the efficacy of drugs, randomized controlled trials (RCT) would have been preferred.[11] In contrast, pharmacokinetic studies do not necessarily require a RCT. As the number of paediatric patients in the Netherlands is small, international collaboration would have been needed to obtain the numbers needed for a RCT within a reasonable time period. These international collaborations where not (yet) established at the start of our studies, yet, there was a clinical urge to initiate a mould-active prophylactic regimen due to the high incidence in the historical cohort. Nonetheless we should reflect on our chosen two-stage design and point out the lessons we have learned. First of all, an initial dose was defined for implementation of the twice-a-week micafunigin regimen. This dose was prospectively analysed and, subsequently, alternative dosing regimens were simulated that could be considered for future research. In parallel, the efficacy of this implemented

twice-a-week dosing regimen was evaluated. With hindsight, by conducting a smaller pharmacokinetic study we would have been able to anticipate on the slower clearance of micafungin in our population and we would have been able to simulate a single optimal dose for efficacy analyses. In our micafungin regimen, this higher exposure was well tolerated and dose adaptation was not necessary. While for other drugs with a narrow therapeutic range a smaller pharmacokinetic study would be needed to facilitate the simulation of an optimal dose, with minimal toxicity, for further efficacy research.

A promising new agent in the pipeline is rezafungin, with an even more patient-friendly dosing schedule for prophylactic purposes in paediatric patients with ALL compared to twice-a-week micafungin. Rezafungin is available as an intravenous formulation, and can be administered once weekly.[11] Drug-drug interactions are not expected.[8] The spectrum of activity seems to be equal to the current echinocandins.[8] Non-inferiority to caspofungin has been demonstrated for candidaemia and invasive candidiasis in adults [12] and pharmacokinetic data in paediatrics is currently being investigated.[8]

Several options to conduct such a trial can be envisioned. Once the pharmacokinetic data in paediatric patients is established and additional insights regarding the correlation between the exposure and the efficacy and safety have been provided in adults, a model-informed dosing regimen could be proposed.[13] With this dose, a rezafungin cohort can be compared to a historical cohort with twice-a-week micafungin. An advantage from this design can be that all patients receive uniform treatment, instead of being allocated to different treatment arms. However, an historical cohort might be more susceptible to bias due to the lack of randomization and controlled study conditions. Also, researchers are restricted to the quality and availability of the existing data.

Alternatively, the efficacy of rezafungin could be studied in a non-inferiority randomized trial compared to twice-a-week micafungin within the Princess Máxima Center. A RCT is still the golden standard for drug efficacy research.[11] Lastly, an adaptive design study could be performed, such as a REMAP (Randomized, Embedded, Multifactorial Adaptive Platform).[14] These trials have become more common during the COVID-19 period, and could also benefit patients of the Princess Máxima Center. This flexible design makes it possible to simultaneously investigate various treatment arms, but also makes it easier to adjust these arms throughout the study. Inferior arms can be early terminated, arms that show efficacy can be closed, and new arms can be introduced, based on predefined criteria.

The disadvantage of the last two study designs might be the number of patients that are needed. With around 100 newly diagnosed patients each year, the numbers are relatively

low. Thus, international collaboration should be considered to facilitate the required number of patients within a more manageable timeframe, moreover, it might be wise to prioritise new drugs considering factors such as the spectrum of activity, the availability of oral formulations, and the frequency of dosing.

Next to rezafungin, also the triazole isavuconazole might be an option for prophylaxis of *Aspergillus* infections during early ALL treatment. The advantage of isavuconazol is that it is available in an oral formulation. Compared to echinocandins, it may exhibit a less favourable profile concerning drug-drug interaction with vincristine and the risk to develop neurotoxicity.[15] However, it has a more favourable profile compared to other triazoles, such as itraconazole, given the moderate impact of isavuconazole on the CYP3A4 enzyme system and thus a moderate impact on the metabolism of vincristine.[16] Recently, isavuconazol has been simulated when coadministered with vincristine. This simulation showed that vincristine exposure was minimally impacted by concomitant use of vincristine.[17] Based on these findings, a drug-drug interaction study for the use of vincristine in combination with isavuconazole without dose adjustments can be suggested. Vincristine administration would preferably be at isavuconazole steady-state conditions. Alternatively, another study suggested that the infusion rate of vincristine might impact the interaction potential with azoles.[18] While the underlying reason for this finding remains unclear, further studies could also investigate vincristine in a one-hour infusion, in combination with isavuconazole, aiming to reduce the risk of vincristine-induced peripheral neuropathy. Furthermore, it is important to assess in parallel the efficacy of vincristine under different modes of administration.

Research infrastructure

One of the strengths of our studies lies in the centralisation of paediatric cancer care in the Princess Máxima Center for paediatric oncology, Utrecht, The Netherlands. In this national cancer center, clinical care and research are closely aligned, providing opportunities for clinical care and research. Conducting our research within this center enabled us to collect robust data in relatively large national paediatric cohorts. Furthermore, patients were treated according to standardized protocols and procedures. This not only led to uniformity of treatment but also provided close monitoring of patients in terms of toxicity. Patient data is entered within a single electronic health care system and data collection is now centrally arranged, streamlining the data collection process for research purposes. Lastly, within our project, there was a close collaboration between the Princess Máxima Center for paediatric oncology, the Radboudumc-CWZ Center of

Expertise in Mycology, Nijmegen, and the University Medical Center Utrecht/Wilhelmina Children's Hospital, Utrecht. This collaborative environment enabled a multidisciplinary approach with combined expertise for both clinical care and research concerning invasive mould disease and laid a foundation for future research initiatives.

In conclusion, in this thesis we delved into a critical side effect of paediatric cancer treatment. The epidemiology and outcome of IMD in paediatric patients with ALL are demonstrated, the pharmacokinetics of novel agents and regimens are provided, and the efficacy of a newly proposed prophylactic regimen has been established. Through these focused studies, this thesis contributes valuable knowledge to the field. It broadens the way for prophylactic and therapeutic approaches within the complex landscape of IMD among paediatric haemato-oncology patients.

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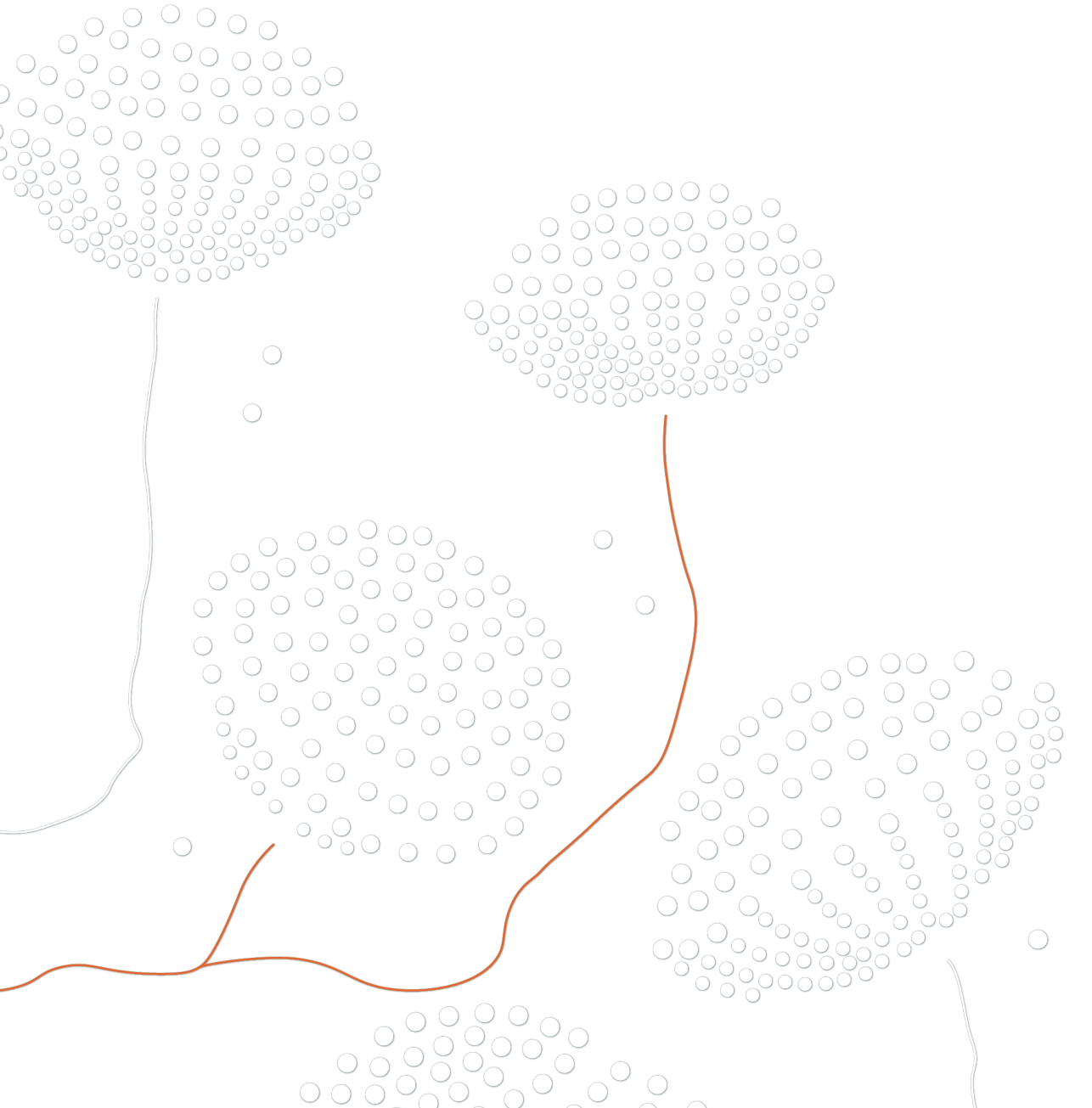

APPENDICES

Nederlandse samenvatting

Invasieve schimmelinfecties zijn infecties die diep in het lichaam kunnen doordringen en levensbedreigend kunnen zijn voor kinderen met een verminderde afweer. Dit geldt bijvoorbeeld voor kinderen met kanker, en met name voor kinderen met leukemie (een vorm van bloedkanker). Het doel van dit onderzoeksproject was het geneesmiddelgedrag te onderzoeken om vervolgens doseringsstrategieën voor medicijnen tegen schimmelinfecties aan te passen en te verbeteren. Hierdoor kunnen schimmelinfecties optimaal voorkomen en behandeld worden bij kinderen met kanker.

Dit proefschrift is ingedeeld in drie delen. In deel I van dit proefschrift wordt gekeken naar hoe vaak kinderen met acute lymfatische leukemie (ALL) schimmelinfecties krijgen, hoe deze schimmelinfecties eruit zien en wat de overlevingskansen zijn (**Hoofdstuk 2**). In deel II van dit proefschrift wordt gekeken naar hoe verschillende geneesmiddelen tegen schimmelinfecties zich gedragen in het lichaam (farmacokinetiek) van kinderen (**Hoofdstuk 3, 4 en 5**). In deel III van dit proefschrift wordt de werking van het antischimmelmedicijn micafungine onderzocht, wanneer het twee keer per week wordt gegeven, ter voorkoming van *Aspergillu*s infecties bij kinderen met ALL (**Hoofdstuk 6**).

In **Hoofdstuk 2** worden de epidemiologie, klinische presentatie, behandeling en uitkomst van invasieve schimmelinfecties bij kinderen (1-18 jaar) met ALL, gediagnostiseerd tussen 2012 en 2018 beschreven. In deze studie zijn 643 patiënten geïncludeerd. De incidentie van waarschijnlijke en bewezen invasieve schimmelinfecties was 7.3%, tijdens de inductie- en eerste consolidatiekuur van de ALL behandeling. De meest voorkomende verwekkers waren *Aspergillus* spp. (89.4%), gevolgd door *Mucorales* spp. (6.4%) en *Alternaria* spp. (4.2%). Kinderen met invasieve schimmelinfecties waren over het algemeen ouder (14 jaar [IQR 7-16]) dan degenen die geen invasieve schimmelinfectie ontwikkelen (5 jaar [IQR 3-10]). Om te screenen naar het voorkomen van invasieve schimmelinfectie wordt veelal gebruik gemaakt van een serum galactomannan test. Galactomannan is een marker voor actieve schimmelinfectie. Het bleek echter, dat een positief resultaat voor serum galactomannan, in slechts 11% van de episodes de aanleiding was voor verder diagnostisch onderzoek. Dit kan de diagnostische waarde van galactomannan screening ter discussie stellen, voornamelijk tijdens kuren waar medicijnen worden gebruikt om schimmelinfecties te voorkomen. De meest voorkomende klinische symptomen bij presentatie waren aanhoudende koorts en ademhalingssymptomen. De longen waren de meest voorkomende plaats van infectie in 94% van de patiënten. De betrokkenheid van het centraal zenuwstelsel was opvallend hoog en werd gediagnosticeerd in 34% van de patiënten. De helft van de patiënten

met betrokkenheid van het centraal zenuwstelsel vertoonde geen symptomen op het moment van de diagnose. De initiële combinatietherapie van liposomaal amfotericine B en voriconazol lijkt gerechtvaardigd gezien de azolenresistentie frequentie van 21% voor *Aspergillus*-isolaten in onze patiëntengroep. Het sterftecijfer 6 weken nadat de diagnose schimmelinfectie was 10.6% en het sterftecijfer na 12 weken was 14.9%. De bovengenoemde bevindingen benadrukken het belang van effectieve strategieën om schimmelinfecties te voorkomen en vroegtijdige beeldvorming van de hersenen bij kinderen met ALL, ook in de afwezigheid van neurologische symptomen.

Hoofdstuk 3 bevat een actueel overzicht van de literatuur over het geneesmiddelgedrag van triazolen in kinderen. Uit dit overzicht blijkt dat het geneesmiddelgedrag van fluconazol uitgebreid is onderzocht in de neonatale populatie en dat het geneesmiddelgedrag van voriconazol uitgebreid is onderzocht bij kinderen en adolescenten. Daarentegen zijn isavuconazol, itraconazol en posaconazol beperkt onderzocht. De gegevens over fluconazol bij kinderen en adolescenten zijn onderbelicht, terwijl voor andere triazolen het geneesmiddelgedrag bij pasgeborenen en zuigelingen dringend moeten worden onderzocht. Isavuconazol is nog beperkt onderzocht in alle groepen. Toekomstige studies zouden zich moeten richten op het geneesmiddelgedrag van deze triazolen en zullen inzicht moeten geven in de biologische beschikbaarheid (ofwel de mate waarin een geneesmiddel voor werking beschikbaar komt) van de aanwezige formuleringen. Verder is er meer informatie nodig over interacties met voedsel of toediening via een sonde, het effect van CYP-genotypes (genen die betrokken zijn bij het verwerken van medicijnen in ons lichaam) en andere afbraak routes. Andere factoren waar rekening mee moet worden gehouden, zijn de ongebonden geneesmiddelconcentraties voor sterk eiwitgebonden medicijnen en de ontwikkeling en het geneesmiddelgedrag van nieuwe orale formuleringen die gemakkelijk kunnen worden toegepast bij kinderen. Daarnaast is er onderzoek nodig naar het geneesmiddelgedrag van triazolen bij ernstig zieke patiënten, de invloed van dialyse, Extra Corporale Membraan Oxygenatie (ECMO) en nier- of leverfunctiestoornissen. Een beter begrip van het geneesmiddelgedrag is noodzakelijk voor optimale klinische zorg en resterende kennishiaten zullen moeten worden opgehelderd.

In **Hoofdstuk 4** wordt de farmacokinetiek van isavuconazol bij Nederlandse kinderen met kanker onderzocht. Uit dit onderzoek is gebleken dat de biologische beschikbaarheid van isavuconazol verminderd was met 41% nadat geopende capsules via een sonde werden toegediend. Daarom zouden artsen moeten overwegen de oplossing voor infusie via de sonde toe te dienen, welke een vergelijkbare opname liet zien vergeleken met

oraal toegediend isavuconazol in een studie met gezonde volwassenen, in combinatie met Therapeutische Drug Monitoring (TDM). Bovendien werd het geneesmiddelgedrag van totaal en ongebonden (werkzaam) isavuconazol gerapporteerd met een vijfvoudige range in de ongebonden fractie. Op dit moment worden voor TDM totale concentraties isavuconazol gemeten. Wanneer de ongebonden fractie echter aanzienlijk varieert, weerspiegelen de totale concentraties de werkzame concentraties van isavuconazol niet meer. We stellen daarom voor om in de toekomst ongebonden isavuconazol concentraties te bepalen voor TDM en om de doelconcentraties die verband houden met werkzaamheid en toxiciteit opnieuw te definiëren op basis van ongebonden isavuconazol concentraties.

In **Hoofdstuk 5** wordt het geneesmiddelgedrag van een tweemaal per week micafungine regime bij Nederlandse kinderen met ALL onderzocht. De gegevens verkregen uit deze grote pediatrische (n=61) populatie werden gecombineerd met een volwassen (n=20) populatie en ondersteunen de rationale van een tweemaal per week micafungine regime. De voorspelde blootstellingen (AUC0-168) voor de 5 mg/kg, 7 mg/kg, 9 mg/kg regimes en het regime met een vaste dosering per gewichtscategorie waren hoger dan de volwassen referentieblootstelling. De hogere blootstelling aan micafungine lijkt te worden veroorzaakt door een klaring (snelheid waarmee het lichaam een geneesmiddel uit het bloed verwijdert) die langzamer was dan verwacht bij deze kinderen met ALL. Onze analyse toonde aan dat een tweemaal per week regime met micafungine in kinderen farmacokinetisch gelijkwaardig is aan een dagelijks micafungine regime in volwassenen.

We evalueerden de werkzaamheid van dit tweemaal per week toegepaste micafungine regime voor *Aspergillus* profylaxe bij Nederlandse kinderen met ALL in **Hoofdstuk 6**. Een tweemaal per week micafungine regime tijdens de inductiekuur van de ALL behandeling resulteerde in een significant lager percentage bewezen en waarschijnlijke invasieve *Aspergillus* infecties tijdens de inductie en eerste consolidatiekuur in het micafungine cohort (1.2%; n=169) vergeleken met het historische cohort (5.8%; n=643) zonder schimmelprofylaxe tijdens de inductiekuur. Bovendien toonden we aan dat deze tweemaal per week toegediende dosis micafungine over het algemeen goed werd verdragen. We concludeerden dat wanneer in een regio *Aspergillus* infecties vaak voorkomen waardoor profylaxe gewenst is, dit micafungine regime gebruikt zou kunnen worden ter voorkoming van invasieve *Aspergillus* infecties tijdens de vroege fase van de ALL behandeling bij kinderen.

Concluderend hebben we in dit proefschrift onderzoek gedaan naar een kritieke bijwerking van de behandeling kanker bij kinderen: invasieve schimmelinfecties. De epidemiologie

en de uitkomst van invasieve schimmelinfecties bij kinderen met ALL zijn beschreven, het geneesmiddelgedrag van nieuwe middelen en behandelingen zijn onderzocht en de werkzaamheid van een nieuw voorgesteld profylactisch regime is vastgesteld. Door deze gerichte studies draagt dit proefschrift bij aan waardevolle kennis op het gebied van infectieprofylaxe en -behandeling binnen de kinderoncologie. Het verbreedt de weg voor profylactische en therapeutische benaderingen binnen het complexe landschap van invasieve schimmelinfecties bij kinderen met kanker.

Curriculum vitae

Werkervaring

Start-up coördinator Trial- en Data Centrum

Prinses Máxima Centrum voor Kinderoncologie (Utrecht) | September 2022 – September 2024

Het coördineren van allerlei werkzaamheden rondom de opstart van het patiëntgebonden onderzoek in het Prinses Máxima Centrum en fungeren als eerste aanspreekpunt voor onderzoekers, service afdelingen, farmaceutische bedrijven en andere betrokkenen bij nieuwe (fase I/II/III) studies.

Promovendus

Prinses Máxima Centrum voor Kinderoncologie (Utrecht) & Radboudumc (Nijmegen) | September 2018 – Januari 2024

Promotieonderzoek gericht op het ontwikkelen en/of optimaliseren van doseringsstrategieën met antifungale middelen voor de profylaxe en behandeling van invasieve schimmel infecties bij pediatrische patiënten met hematologische maligniteiten.

(Co)promotoren: Prof. Dr. L.J. Bont (UMC Utrecht), Prof. Dr. W.J.E. Tissing (Prinses Máxima Centrum), Dr. T.F.W. Wolfs (Wilhelmina Kinderziekenhuis) en Dr. R.J. Brüggemann (Radboudumc).

Opleiding

Master farmacie

Universiteit van Utrecht | 2014 – 2018

Master thesis: Bury D, Ter Heine R, van de Garde EMW, Nijziel MR, Grouls RJ, Deenen MJ. The effect of neutropenia on the clinical pharmacokinetics of vancomycin in adults. Eur J Clin Pharmacol. 2019;75(7):921-928. (DOI:10.1007/s00228-019-02657-6)

Bachelor farmacie

Universiteit van Utrecht | 2010 – 2014

Awards

Best abstract

Nederlandse Vereniging van Ziekenhuisapothekers (NVZA) | Bunnik 2017

Bury D, ter Heine R, van de Garde EMW, Grouls RJ, Deenen MJ. A 25% higher vancomycin maintenance dose is required in neutropenic hematologic patients.

List of publications

This thesis

Bury D, Parmentier CEJ, Tissing WJE, Pieters R, Bont LJ, Brüggemann RJ, Wolfs TFW. Clinical presentation and outcome of invasive mould disease in paediatric patients with acute lymphoblastic leukaemia. *EJC Paediatric Oncology 2024 Jan;3:100143 (DOI*: *10.1016/j.ejcped.2024.100143)*

Bury D, Wolfs TFW, Ter Heine R, Muilwijk EW, van der Elst KCM, Tissing WJE, Brüggemann RJ. Pharmacokinetic investigations of isavuconazole in paediatric cancer patients show reduced exposure of isavuconazole after opening capsules for administration via a nasogastric tube. J Antimicrob Chemother. 2023 Dec 1;78(12):2886-2889. (DOI: 10.1093/jac/dkad324. PMID: 37864491)

Bury D, Wolfs TFW, Muilwijk EW, Fiocco M, Pieters R, Brüggemann RJ, Tissing WJE. Micafungin twice-a-week for prophylaxis of invasive *Aspergillus* infections in children with acute lymphoblastic leukaemia: A controlled cohort study. Int J Antimicrob Agents. 2024 Jan;63(1):107058. (DOI: 10.1016/j.ijantimicag.2023.107058. PMID: 38081549)

Bury D, Wolfs TFW, Ter Heine R, Muilwijk EW, Tissing WJE, Brüggemann RJ. Pharmacokinetic evaluation of twice-a-week micafungin for prophylaxis of invasive fungal disease in children with acute lymphoblastic leukaemia: a prospective observational cohort study. J Antimicrob Chemother. 2022 Feb 23;77(3):699-703. (DOI: 10.1093/jac/dkab467. PMID: 34939125)

Bury D, Tissing WJE, Muilwijk EW, Wolfs TFW, Brüggemann RJ. Clinical Pharmacokinetics of Triazoles in Pediatric Patients. Clin Pharmacokinet. 2021; 60(9): 1103–1147. (DOI: 10.1007/s40262-021-00994-3. PMID: 34002355; PMCID: PMC8416858)

PhD portfolio

Courses and workshops	Year
Nascholing ‘Professionals in de kinderoncologie’	2018
BROK course	2018
De 24-uur van Woudschoten	2018
Clinical mycology (Radboudumc) - 9-day course (excl. practical work and exam)	2019
Art of presenting science	2019
Writing for Academic publication	2019
Statistics for PhD candidates using SPSS	2019
SamenWeten: Ga eens buiten je boekje	2020
Scientific integrity course	2020
Pediatric Dose Selection Public Workshop - FDA	2020
This Thing Called Science (Online)	2021
Supervised reviewing of manuscripts	2021
CTO introduction course ‘Hot and Happening’	2021
Crash course mycology	2021
Re-registration BROK	2022
Presentations	**Year**
Oral, Nederlandse Vereniging voor klinische farmacologie en biofarmacie (NVKFB) - online	2020
Oral, Princess Máxima Research Meeting	2021
Oral, best abstract, Nederlandse Vereniging van Ziekenhuisapothekers (NVZA)	2022
Oral, Princess Máxima Research Meeting	2022
Oral, Mini-symposium infectious diseases	2023
E-Poster, European Society for Paediatric Infectious Diseases (ESPID)	2020
Poster, Multinational Association of Supportive Care in Cancer (MASCC) - presented by dr. R.J. Brüggemann	2021
Poster, International Society of Paediatric Oncology (SIOP)	2022
(Inter)national conferences and research retreats	**Year**
European Congress of Clinical Microbiology & Infectious Diseases (ECCMID)	2019
Trends in Medical Mycology (TIMM)	2019
CTO PhD retreat	2019
Research retreat Princess Máxima Center	2019
European Society for Paediatric Infectious Diseases (ESPID)	2020
CTO PhD retreat (including organization)	2020
Research retreat Princess Máxima Center	2021
Trends in Medical Mycology (TIMM)	2021
European Congress of Clinical Microbiology & Infectious Diseases (ECCMID) - online	2021
NVMy Fungal Update Meeting	2022
European Congress of Clinical Microbiology & Infectious Diseases (ECCMID)	2022

CTO PhD retreat	2022
International Society of Paediatric Oncology (SIOP)	2022
Research retreat Princess Máxima Center	2022
Nederlandse Vereniging van Ziekenhuisapothekers (NVZA)	2022
Supervising	**Year**
Corline Parmentier, Master student Medicine	2019
Charlotte Commijs, Master student Medicine	2020

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Terwijl ik deze laatste pagina van mijn proefschrift bereik, dringt het tot me door dat dit tegelijkertijd ook het einde markeert van een ongelofelijke reis - hoogtepunten, enorme uitdagingen en groei. Een reis die zonder velen van jullie niet mogelijk zou zijn geweest. Ik ben dan ook ontzettend dankbaar voor iedereen die, op welke manier dan ook, hieraan heeft bijgedragen. Met heel mijn hart wil ik jullie bedanken voor jullie steun en liefde gedurende dit promotietraject.