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REVIEW ARTICLE

Clinical Pharmacokinetics of Triazoles in Pediatric Patients

Didi Bury[1,2] · Wim J. E. Tissing[1,3] · Eline W. Muilwijk[1,4] · Tom F. W. Wolfs[5,6] · Roger J. Brüggemann[1,2,7]

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Abstract
Triazoles represent an important class of antifungal drugs in the prophylaxis and treatment of invasive fungal disease in pediatric patients. Understanding the pharmacokinetics of triazoles in children is crucial to providing optimal care for this vulnerable population. While the pharmacokinetics is extensively studied in adult populations, knowledge on 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 the 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 summarized 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 pediatric patients.

1 Introduction

Immunocompromised pediatric patients are at high risk for invasive fungal disease (IFD). Although advances have been made in the management of IFD, the incidence and mortality rates are still high whereas treatment options remain limited and challenging. Triazoles represent the most important class of antifungal drugs for the 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 the pharmacokinetics (PK) of these triazoles in pediatric 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 pediatric patients is limited. Pediatric 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 pediatric populations and summarizes factors that have to be taken into account to select the optimal dose.

2 Search Methodology

Relevant articles that describe the PK of triazoles in pediatric patients were searched until 26 November, 2020 using the databases PubMed and Embase. A detailed description of the literature search strategy is given in the Electronic Supplementary Material. Conference abstracts and unpublished

✉ Roger J. Brüggemann
Roger.Bruggemann@radboudumc.nl

1 Department of Supportive Care, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

2 Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

3 Department of Pediatric Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

4 Department of Pharmacy, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

5 Department of Infectious Diseases, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

6 Department of Infectious Diseases, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

7 Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands

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 pediatric population despite its limited clinical use in these populations.

Isavuconazole, posaconazole, and itraconazole pharmacokinetics are studied to a limited extend in pediatric populations. To our opinion, specifically isavuconazole and posaconazole pharmacokinetics need to be investigated, as these drugs are frequently used in the hemato-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, extracorporeal membrane oxygenation as well as renal or hepatic impairment is lacking in most cases and should warrant further exploration.

data from conference proceedings were not included in this review.

The order of appearance of each triazole in this article is in the order of appearances of market introduction. This emphasizes 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 pediatric PK for both non-compartmental analyses (NCA) and population PK analyses.

3 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.

4 Fluconazole

The US 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 pediatric patients aged 0–17 years for the 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

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

	Fluconazole[a]	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
CYP2C9	Moderate inhibitor [4, 82]				Substrate[b]/weak inhibitor [5, 82]
CYP2C19	Strong inhibitor [4, 82]				Moderate substrate/weak inhibitor [5, 82]
CYP3A4/A5	Moderate inhibitor [4, 82]	Substrate[b]/moderate inhibitor [7]	Substrate[b]/strong inhibitor [6, 82]	Strong inhibitor [8, 82]	Substrate[b]/strong inhibitor [5, 82]
UGT		Substrate[b] [7]		Substrate/inhibitor[b] [83]	
P-gp		Mild inhibitor [7]	Inhibitor[b] [6, 82]	Substrate/inhibitor[b] [83]	

CYP cytochrome P450, *FDA* US Food and Drug Administration, *P-gp* P-glycoprotein, *UGT* uridine diphosphate glucuronosyltransferase

[a]Renal excretion

[b]Substrate sensitivity/inhibition mentioned in the FDA label and/or FDA drug interaction and labeling list, but the potency of sensitivity/inhibition is not mentioned and therefore not further specified in this table

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

		Europe[c] [10]		FDA [4]		ESCMID [2]		IDSA [3]	
		Prophylaxis	Treatment	Prophylaxis	Treatment	Prophylaxis	Treatment	Prophylaxis	Treatment
Neonates	Preterm neonates (PNA 0–14 days)			3–12 mg/kg every 72 hours					
	Preterm neonates (PNA > 14 days)			3–12 mg/kg every 24 hours					
	Term neonates (PNA 0–14 days)	3–12 mg/kg (maximum 12 mg/kg) every 72 hours[a]	(Loading dose 6 mg/kg, on day 1)[a] 3–12 mg/kg (maximum 12 mg/kg) every 72 hours[a]						
	Term neonates (PNA 15–27 days)	3–12 mg/kg (maximum 12 mg/kg) every 48 hours[a]	(Loading dose 6 mg/kg, on day 1)[a] 3–12 mg/kg (maximum 12 mg/kg) every 48 hours[a]						
	Neonates (< 1000 g)					3–6 mg/kg twice weekly[b]		3–6 mg/kg twice weekly[b]	
	Neonates (no PNA or GA reported)						(Loading dose 25 mg/kg)[a] 12 mg/kg every 24 hours[a]		12 mg/kg every 24 hours
Infants/children/adolescents	Age: 28 days to 11 years	3–12 mg/kg (maximum 400 mg/day) every 24 hours[a]	(Loading dose 6 mg/kg, maximum 400 mg, on day 1)[a] 3–12 mg/kg (maximum 400 mg) every 24 hours[a]						
	Age: 12–18 years	3–12 mg/kg (maximum 400 mg) every 24 hours[a]	(Loading dose 6–12 mg/kg, maximum 800 mg, on day 1)[a] 3–12 mg/kg (maximum 800 mg) every 24 hours[a]						
	Infants (no age range reported)						(Loading dose 25 mg/kg)[a] 12 mg/kg (maximum 400 mg) every 24 hours[a]		

Table 2 (continued)

	Europe[c] [10]		FDA [4]		ESCMID [2]		IDSA [3]	
	Prophylaxis	Treatment	Prophylaxis	Treatment	Prophylaxis	Treatment	Prophylaxis	Treatment
Children (no age range reported)			6–12 mg/kg every (maximum 600 mg) 24 hours[a]	(Loading dose 6–12 mg/kg, maximum 600 mg)[a] 3–12 mg/kg (maximum 600 mg) every 24 hours[a]	8–12 mg/kg (maximum 400 mg) every 24 hours			12 mg/kg every 24 hours

ESCMID European Society of Clinical Microbiology and Infectious Diseases, *FDA* US Food and Drug Administration, *IDSA* Infectious Diseases Society of America, *GA* gestational age, *PNA* postnatal age

[a]Fluconazole (loading) dose is dependent on type, severity, and localization of the infection

[b]Fluconazole prophylaxis is dependent on risk stratification strategy (incidence rate of *Candida* infection and neonate risk factors)

[c]Dutch label

Clinical Microbiology and Infectious Diseases (ESCMID), and the Infectious Diseases Society of America 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, such as cerebrospinal fluid, sputum, saliva, urine, and skin [11]. The affinity of fluconazole for plasma proteins is low (10–12%). Fluconazole is minimally metabolized (~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].

4.1 Non-Compartmental Analysis of Fluconazole PK in Pediatric Patients

Six studies described NCA of fluconazole PK in pediatric 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 pharmacokinetic results is given in Table 3. The neonatal study included 12 premature neonates aged < 24 h after birth receiving fluconazole intravenously in a dose of 6 mg/kg with a dose interval of 72 h [12]. The five studies in preterm and term infants and children included patients with hematological or non-hematological 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 were 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 2 weeks after birth, the V_d of fluconazole in premature neonates almost doubled and CL increased more than two times [12]. After 2 weeks of life, the V_d of premature neonates was found to be higher compared with 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 aged < 12 years need adequate loading doses compared to older children and adults. The higher V_d

of fluconazole in premature neonates vs children and adults might be explained by the 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 pediatric PD population [14]. To our knowledge, no other disease variables, such as HIV, have been found to alter the exposure of fluconazole [15–17].

4.2 Population Pharmacokinetic Analysis of Fluconazole in Pediatric Patients

Nine 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 of these studies pooled data from three previously reported studies [26]. A detailed overview of the dosing regimens and fluconazole pharmacokinetic 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 hemato-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 from 90.9 to 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) was from 0.538 to 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], 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], serum creatinine [24, 25], 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 a 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 a 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 pediatric ECMO patients compared with 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 for an adequate loading dose of fluconazole in pediatric ECMO patients.

4.3 Physiologically Based PK of Fluconazole

Two studies have obtained interesting pharmacokinetic information with physiologically based pharmacokinetic 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 g) with a median PNA of 21 days (range 3–93 days) and cerebrospinal fluid samples of 22 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 edema disease state of ECMO patients was added to the model and the authors suggested that edema contributes to lower fluconazole exposure [31]

Table 3 Non-compartmental analyses of fluconazole

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters							References
						C_{max}	C_{min}	T_{max}	AUC	$T_{1/2}$	CL	V_d	
Premature neonates aged < 24 h after birth	6 mg/kg IV with a dose interval of 72 h	IV	NR	12	FD day 1	Mean (range)[a] 5.5 mg/L (3.7–10.2) C_{max}	NR	Mean (range) 2.2 h (0.2–6.6)	NR	Mean (range) 88.6 h (43.3–187.3)	Mean (range)[a] 0.011 L/h/kg (0.005–0.017)	Mean (range) 1.18 L/kg (1.05–1.48)	[12]
			NR		MD day 7 day 13	Mean (range)[a] 12.8 mg/L (6.0–17.8) 10.0 mg/L (6.0–14.1) C_{max}	NR	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)[a] 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)	
Premature infants < 3 months of age	6 mg/kg daily	IV ($N = 2$) and PO ($N = 6$) [suspension]	NR	6	SD	Median (range)[a] 9.6 mg/L (6.0–13.5) C_{max}	NR	NR	Median (range)[a] 412 mg*h/L (340–636) AUC_{inf}	NR	Median (range)[a] 0.014 L/h/kg (0.007–0.017) CL/F	NR	[13]
Children with or without 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	NR	NR	Mean (STDV) 72.4 h (9.7)	Mean (STDV)[a] 0.018 L/h/kg (0.008) CL_{plasma} 0.014 L/h/kg (0.005) CL_{pd} (24 h peritoneal clearance)	Mean (STDV) 1.39 L/kg (0.22)	[14]
			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	Mea n(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	NR	NR	Mean (STDV) 30.9 h (4.0)	Mean (STDV)[a] 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)	

Table 3 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters							References
						C_{max}	C_{min}	T_{max}	AUC	$T_{1/2}$	CL	V_d	
Immunocompromised children (congenital disease, HIV, malignant disease or prematurity) aged 0.25–16 years	2, 3, or 8 mg/kg daily	IV and PO	NR	101[c]	NR 0.25–2 years 2–12 years ≥12 years 2 mg/kg IV	NR	NR	NR	Mean (STDV)[a] NR 73.7 mg*h/L (38.6) 92.2 mg*h/L[b] 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]
					0.25–2 years 2–12 years ≥12 years 2 mg/kg PO	NR	NR	NR	Mean (STDV)[a] 56.2 mg*h/L (12.0) 103.6 mg*h/L (29.7) 74.2 mg*h/L[b] AUC_{inf}				
					0.25–2 years 2–12 years ≥12 years 3 mg/kg IV	NR	NR	NR	Mean (STDV)[a] 110.1 mg*h/L (20.2) NR NR $AUC_{0–96}$				
					0.25–2 years 2-12 years ≥12 years 3 mg/kg PO	NR	NR	NR	Mean (STDV)[a] 51.4 mg*h/L[b] 62.8 mg*h/L (15.8) 52.8 mg*h/L[b] $AUC_{0–48}$				
					0.25–2 years 2–12 years ≥12 years 8 mg/kg IV	NR	NR	NR	Mean (STDV)[a] NR 218.2 mg*h/L (77.1) 230.9 mg*h/L (94.2) AUC_{inf}				
					0.25–2 years 2–12 years ≥12 years 8 mg/kg PO	NR	NR	NR	Mean (STDV)[a] 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	Pharmacokinetic parameters							References
						C_{max}	C_{min}	T_{max}	AUC	$T_{1/2}$	CL	V_d	
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)[a] 2.95 mg/L (2.31–4.40) 10.3 mg/L (5.44–12.14) C_{max}	NR	Median (range)[a] 2.0 h (0.5–2.0) 1.0 h (1.0–4.0)	Median (range)[a] 48.3 mg*h/L (40.6–58.2) 205.9 mg*h/L (133.9–241.9) AUC_{0-24} Median(range)[a] 97.8 mg*h/L (84.9–135.9) 413.5 mg*h/L (330.2–684.3) AUC_{inf}	Median (range)[a] 27.1 h (19.8–34.9) 32.1 h (25.6–42.3)	NR	NR	[16]
Children with neoplastic disease aged 5–15 years	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)[a] 3.9 mg/L (0.20) 6.4 mg/L (0.31) 9.5 mg/L (0.14) C_{max}	Mean (SEM)[a] 1.7 mg/L (0.09) 2.0 mg/L (0.13) 2.7 mg/L (0.14) C_{min}	NR	Mean (SEM)[a] 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]
			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)[a] 5.4 mg/L (0.39) 10.5 mg/L (0.69) 14.3 mg/L (0.35) C_{max}	Mean(SEM)[a] 2.5 mg/L (0.30) 3.2 mg/L (0.55) 5.5 mg/L (0.29) C_{min}	NR	Mean (SEM)[a] 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)[a] 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	26	Overall	NR	NR	NR	NR	Mean (SEM) 17.4 h (1.1)	Mean (SEM)[a] 0.035 L/h/kg (0.0025)	Mean (SEM) 0.86 L/kg (0.4)	

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

[a]Values recalculated/adjusted from the original paper to create uniformity of units (when individual values were reported, the median was calculated from these values)

[b]Data only available from one patient

[c]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 analyzed 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								References
						AUC	$T_{1/2}$	CL	V_1	*Q*	*V*2	K_a	*F*	
Preterm neonates at risk for invasive candidiasis with a median PNA of 3 days	3 mg/kg with a dose interval of 72 h	IV and PO (orogastric tube)	Median (range) 1.1 kg (0.9–1.3)	75	MD	NR	NR	$0.0197 \times (WT/1.00)^{0.746} \times (eGFR/25.0)^{0.463}$	$1.04 \times (WT/1.00)^{a}$	NR	NR	Estimate (RSE%) 0.538 1/h (18.5)	Estimate (RSE%) 0.909 (7.03)	[20]
Preterm neonates < 750 g with a median PNA of 23 days	6 mg/kg twice weekly	IV and PO (suspension)	Median (range)[c] 0.71 kg (0.35–2.7)	141	MD	NR	NR	$0.0127 \times (SCR/0.8)^{0.41} \times (PMA/28)^{2.05b}$	1.00^{b}	NR	NR	Point estimate (SEE) 0.96 1/h (0.25)	Point estimate (SEE) 1.00 (0.065)	[21]
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)[c] 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	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]

Table 4 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters								References
						AUC	$T_{1/2}$	CL	V_1	*Q*	*V*2	K_a	*F*	
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)[c] 90.2 mg*h/L (9.0) AUC_{inf}	Mean (STDV) 22.5 h (2.2)	Mean (SEM)[c] 0.0378 L/h/kg (0.0036)	Mean (SEM) 1.17 L/kg (0.14)	NR	NR		NR	[27]
Preterm and term infants at risk for invasive candidiasis with a 23- to 42-week gestation and aged < 120 days	Dosing range 3–12 mg/kg/dose	IV	Median (range)[c] 1.020 kg (0.451–7.125)	55	MD	NR	NR	$0.015 \times (WT/1.00)^{0.75} \times (BGA/26)^{1.739} \times (PNA/2)^{0.237} \times (SCR/1)^{(-4.896)(CR)d}$	$1.024 \times (WT/1.00)^{1}$	NR	NR	NR	NR	[23]

Table 4 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters								References
						AUC	$T_{1/2}$	CL	V_1	*Q*	*V*2	K_a	*F*	
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}	Median (IQR) 56 h (26–80)	Median (IQR)[c] 0.016 L/h/kg (0.013–0.021)	Median (IQR)[c] 1.051 L/kg (0.858–1.461)	NR	NR	NR	NR	[24]
Infants supported with ECMO, with a 23- to 41-week gestation and aged < 120 days	IV prophylaxis: 25 mg/kg once a week Followed by IV treatment: 12 mg/kg daily in patients with suspected or known fungal disease[g]	IV	Median (IQR) 3.2 kg (2.6–3.4)	10	FD	Median (IQR) 322 mg*h/L (307–343) AUC_{0-24}	Median (IQR) 60 h (47–76)	Median (IQR)[c,f] 0.017 L/h/kg (0.014–0.022)	Median (IQR)[f] 1.5 L/kg (1.3–1.7)	NR	NR	NR	NR	[25]
					MD	Median (IQR) 352 mg*h/L (344–399) AUC_{0-24}	Median (IQR) 56 h (37–92)	Median (IQR)[c f] 0.022 L/h/kg (0.011–0.033)	Median (IQR)[f] 1.9 L/kg (1.4–2.2)	NR	NR	NR	NR	

Table 4 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters								References
						AUC	$T_{1/2}$	CL	V_1	*Q*	*V2*	K_a	*F*	
See reference [23–25]. From study [24] only patients with a GA of ≥ 36 weeks were included	See reference [23], [24], and [25]	IV	Median (range) 3.4 kg (1.9–77)	40 (21 with ECMO)[g]	FD and MD	NR	NR	$0.019 \times WT \times (SCR/0.4)^{-0.29}$	$0.93 \times WT \times 1.4^{ECMOe}$	NR	NR	NR	NR	[26]
Immunocompromised hemato-oncology patients aged 1.8–15.9 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	Mean (STDV) 15.63 h (3.21)	Mean (STDV)[c] 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]

AUC area under the curve, *CGA* corrected gestational age, *CI* confidence interval, *CL* clearance, *ECMO* extracorporeal membrane oxygenation, *F* bioavailability, *FD* first dose, *h* hours, *IV* intravenous, K_a rate of oral bioavailability, *MD* multiple dose, *N* total patients, *NR* not reported, *PNA* postnatal age, *PO* 'per os' (oral administration), *Q* intercompartmental clearance, *RSE* relative standard error, *SCR* serum creatinine, *SD* single dose, *SEE* standard error of estimate, $t_{1/2}$ elimination half-life, *V1* volume of distribution in the central compartment, *V2* volume of distribution of the peripheral compartment, V_d volume of distribution, $V_{d,SS}$ volume of distribution at steady state, *WT* weight

[a]Fixed or estimated value of exponent used for allometric scaling of volume of distribution was not reported

[b]Unclear how WT was standardized in this equation

[c]Values recalculated/adjusted from original paper to create uniformity of units

[d]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

[e]ECMO = 1 or 0

[f]Only one patient received fluconazole treatment

[g]Number of ECMO patients reported in this pooled study does not add up with the number of ECMO patients in the individual studies

Table 5 Pharmacokinetic models of fluconazole

Population	Subjects, *N*	Samples, *N*	Program	Covariates tested	Compartments	PO/IV	Covariates in final model					References
							CL	*V*1	*Q*	*V*2	$T_{1/2}$	
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	1, with first-order absorption	IV and PO	eGFR with estimated exponent, allometrically scaled WT with estimated exponent. Both normalized to a standard individual	Allometrically scaled WT with fixed exponent, normalized to a standard individual	NR	NR	NR	[20]
Preterm neonates <750 g 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)	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 normalized to a standard individual	Allometrically scaled WT with a fixed exponent of 1 and normalized to a standard individual	NR	NR	NR	[21]
Preterm and term neonates and infants with suspected or proven candidiasis and a 23- to 40-week gestation and a mean PNA range 13.5 days	18	82	NONMEM	WT, PMA	1	IV	WT[a]	NR	NR	NR	NR	[22]
Neonates and infants with oral candidiasis or at risk for invasive fungal disease aged between 9 days and 4.4 months	14	NR	TOPFIT	Age	1	IV	NR	Age	NR	NR	Age	[27]

Table 5 (continued)

Population	Subjects, *N*	Samples, *N*	Program	Covariates tested	Compartments	PO/IV	Covariates in final model					References
							CL	*V*1	*Q*	*V*2	$T_{1/2}$	
Preterm and term infants at risk for invasive candidiasis 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	1	IV	Allometrically scaled WT with a fixed exponent of 0.75, BGA, PNA, and SCR. All normalized to a standard individual	Allometrically scaled weight with a fixed exponent of 1 and normalized to a standard individual	NR	NR	NR	[23]
Hospitalized neonates and infants at risk for invasive fungal disease and a median gestation age of 37 weeks aged < 60 days	8	57	WinNonLin	SCR (linear regression analysis)	1	IV	SCR	NR	NR	NR	NR	[24]
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)	1	IV	SCR	ECMO	NR	NR	NR	[25]
See reference [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 required to prime the ECMO circuit, ratio of blood prime volume to the estimated native blood volume of the child, hemofiltration, use of CVVHD, SCR, ALB, AST, ALT, PNA, sex, race	1	IV	Exponent for creatinine, WT	Coefficient for ECMO, WT	NR	NR	NR	[26]

Table 5 (continued)

Population	Subjects, *N*	Samples, *N*	Program	Covariates tested	Compartments	PO/IV	Covariates in final model						References
							CL	*V1*	*Q*	*V2*	$T_{1/2}$		
Immunocompromised hematooncology patients aged 1.8–15.9 years	10	NR	NONMEM	Age, WT, HT, BSA, creatinine clearance (linear regression analysis)	2, with first-order absorption	IV and PO	BSA	WT[b]	NR	NR	NR		[28]

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

[a]WT is included as covariate on fluconazole CL; however, the covariate equation was not reported

[b]V_{dss} was best correlated with BSA

4.4 Summary of Findings and Recommendations

Pharmacokinetic data of fluconazole in neonates and infants are abundant, and pharmacokinetic 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 pediatric 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 pediatric patients is comparable to the *F* described in adults, which suggests that different formulations of fluconazole are interchangeable in pediatric patients. Most of these studies included the suspension as oral formulation, data on *F* of other oral formulations are very limited in pediatric patients.

Non-compartmental analyses report a higher V_d in preterm neonates compared with 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 CL in children but higher as compared to CL in adults. These results imply that higher maintenance doses or shorter dosing intervals are needed in preterm neonates and children. Non-compartmental analyses in pediatric 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 pediatric population.

Population PK studies report that allometrically scaled bodyweight and ECMO are significant covariates on V_d. As a consequence, pediatric 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 standardized 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 Infectious Diseases Society of America 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.

5 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 pediatric patients aged < 18 years [6, 33]. However, the pediatric ESCMID-ECMM guideline for invasive aspergillosis and the pediatric ESCMID guideline for invasive candidiasis recommend a dose of 2.5 mg/kg twice daily of the oral solution for the purpose of mold 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 with 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 the 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 the urine (35%) and feces (54%). Mean CL of itraconazole in adults is 16.68 L/h [6].

5.1 Non-Compartmental Analysis of Itraconazole PK in Pediatric Patients

To our knowledge, there are no NCA reports of itraconazole PK described in neonates. Six studies performed NCA of itraconazole in infants, children, and adolescents aged 0.5–17 years at risk of mucosal fungal infection or IFD. A detailed overview of the dosing regimens and itraconazole pharmacokinetic results is given in Table 6. Patients with hematological and non-hematological malignancies, liver transplantation, respiratory tract infections, HIV, cystic fibrosis (CF), other infections/diseases, or undergoing hematopoietic 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 were from 2.5 to 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 pediatric 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 of itraconazole twice daily compared with other pediatric populations [41, 44]. Higher dosages than 2.5 mg/kg twice daily might be needed in pediatric patients with CF.

5.2 Population Pharmacokinetic Analysis of Itraconazole in Pediatric Patients

Two population pharmacokinetic studies in pediatric 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 summarized in Table 8.

In 33 patients at risk for IFD aged 0.5–17 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 0.4–30 years, including five adult

Table 6 Non-compartmental analyses of itraconazole

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters							References
						C_{max}	C	T_{max}	AUC	$T_{1/2}$	CL	V_d	
Children at risk for IFD aged 0.5–17 years	2.5 mg/kg	IV	Mean (STDV) 31.1 kg (22.7)	33	SD 0.5–2 years > 2–6 years > 6–12 years > 12–16 years Overall	ITZ[a] Mean (STDV) 0.827 mg/L (0.859) 1.553 mg/L (0.918) 0.785 mg/L (0.301) 0.806 mg/L (0.381) 1.015 mg/L (0.692) C_{max}	NR	NR	ITZ[a] Mean (STDV) 2.121 mg*h/L (1.231) 9.510 mg*h/L (11.316) 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[a] 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) 0.703 L/h/kg (0.499)	ITZ[a] 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]
					0.5–2 years > 2–6 years > 6–12 years > 12–16 years Overall	H-ITZ[a] Mean (STDV) 0.265 mg/L (0.257) 0.299 mg/L (0.162) 0.277 mg/L (0.104) 0.321 mg/L (0.093) 0.293 mg/L (0.133) C_{max}	NR	NR	H-ITZ[a] 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	
HSCT patients aged 0.9–23 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[b] 29 kg	6	MD (after third IV dose)	ITZ[a] Mean (STDV) 4.429 mg/L (1.072) $C_{max,SS}$	NR	NR	ITZ[a] Mean (STDV) 42.837 mg*h/L (24.746) $AUC_{0-24,SS}$	ITZ Mean (STDV) 39.5 h (33.5)	ITZ[a] Mean (STDV) 0.1313 L/h/kg (0.05652) CL_{SS}	ITZ[a] Mean (STDV) 6.959 L/kg (6.897) V_{SS}	[40]
						H-ITZ[a] Mean (STDV) 3.778 mg/L (0.722) $C_{max,SS}$	NR	H-ITZ Median(range) 4 h (1.0-7.6)	H-ITZ[a] Mean (STDV) 63.094 mg*h/L (19.255) $AUC_{0-24\,SS}$	H-ITZ Mean (STDV) 51.0 h (17.9)	H-ITZ[a] Mean (STDV) 0.07969 L/h/kg (0.02662) CL_{SS}	H-ITZ[a] Mean (STDV) 5.659 L/kg (2.341) V_{SS}	

Table 6 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters							References
						C_{max}	C	T_{max}	AUC	$T_{1/2}$	CL	V_d	
CF patients aged < 16 years	2.5 mg/kg every 12 h for 14 days	PO (solution)	Median(range) 16.6 kg/m^2 (15–19.7) BMI	5	FD Day 1	ITZ[a] Mean (STDV) 0.133 mg/L (0.135) C_{max}	NR	NR	ITZ[a] Mean (STDV) 0.433 mg*h/L (0.358) AUC_{0-12}	NR	NR	NR	[41]
						H-ITZ[a] Mean (STDV) 0.230 mg/mL (0.141) C_{max}	NR	NR	H-ITZ[a] Mean (STDV) 1.168 mg*h/L (0.707) AUC_{0-12}	NR	NR	NR	
					MD Day 14	ITZ[a] Mean (STDV) 0.404 mg/mL (0.268) C_{max}	ITZ[a] Mean (STDV) 0.119 mg/L (0.0834) C_{min} Mean (STDV) 0.191 mg/L (0.110) Css,av		ITZ[a] Mean (STDV) 2.298 mg*h/LL (1.322) AUC_{0-12}	NR	NR	NR	
						H-ITZ[a] Mean (STDV) 0.550 mg/mL (0.240) C_{max}	H-ITZ[a] Mean (STDV) 0.276 mg/L (0.161) C_{min} Mean (STDV) 0.400 ng/mL (0.216) $C_{ss,av}$		H-ITZ[a] Mean (STDV) 4.792 mg*h/L (2.594) AUC_{0-12}	NR	NR	NR	

Table 6 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters							References
						C_{max}	C	T_{max}	AUC	$T_{1/2}$	CL	V_d	
Infants and children aged 0.5–12 years with hematological 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[a] Mean (STDV) 0.138 mg/L (0.091) 0.314 mg/L (0.105) 0.298 mg/L (0.292) C_{max}	NR	NR	ITZ[a] 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]
					0.5–2 years 2–5 years 5–12 years	H-ITZ[a] Mean (STDV) 0.179 mg/L (0.101) 0.493 mg/L (0.106) 0.447 mg/L (0.365) C_{max}	NR	NR	H-ITZ[a] 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	
					MD Day 14 0.5–2 years 2–5 years 5–12 years	ITZ[a] Mean (STDV) 0.571 mg/L (0.416) 0.534 mg/L (0.431) 0.631 mg/L (0.358) C_{max}	ITZ[a] Mean (STDV) 0.159 ng/mL (0.218) 0.179 ng/mL (0.101) 0.223 ng/mL (0.145) pre-dose concentration		ITZ[a] 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	
					0.5–2 years 2–5 years 5–12 years	H-ITZ[a] Mean (STDV) 0.690 mg/L (0.445) 0.687 mg/L (0.419) 0.699 mg/L (0.234) C_{max}	H-ITZ[a] Mean (STDV) 0.308 mg/L (0.436) 0.487 mg/L (0.314) 0.437 mg/L (0.246) pre-dose concentration		H-ITZ[a] 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	

Table 6 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters							References
						C_{max}	C	T_{max}	AUC	$T_{1/2}$	CL	V_d	
Cancer patients at risk for IFD aged 2–12 years	2.5 mg/kg PO every 12 h	PO (oral solution)	NR	17	MD 2–5 years 6–12 years 2–5 years 6–12 years 2–5 years 6–12 years	ITZ[a] Mean (STDV) 0.599 mg/mL (0.231) 1.090 mg/L (0.383) $C_{max\ 4h}$, day 7 ITZ[a] Mean (STDV) 1.024 mg/L (0.351) 1.524 mg/L (0.770) $C_{max\ 4h}$, day 15	ITZ[a] Mean (STDV) 0.439 mg/L (0.255) 0.674 mg/L (0.285) $C_{min\ 12h}$, day 7 ITZ[a] Mean (STDV) 0.711 mg/L (0.251) 1.072 mg/L (0.408) $C_{min\ 12h}$, day 15 ITZ[a] Mean (STDV) 0.877 mg/L (0.248) 1.085 mg/L (0.329) C_{ssmin}	ITZ Mean (STDV) 13 days (4) 12 days (6) T_{Css}	ITZ[a] Mean (STDV) 16.128 mg*h/L (3.12) 20.496 mg*h/L (7.25) $AUC_{min/d}$	NR	NR	NR	[43]
					MD 2–5 years 6–12 years 2–5 years 6–12 years 2–5 years 6–12 years	H-ITZ[a] Mean (STDV) 1.008 mg/L (0.341) 1.658 mg/L (0.426) $C_{max\ 4h}$, day 7 H-ITZ[a] Mean (STDV) 1.358 mg/L (0.373) 2.180 mg/L (0.753) $C_{max\ 4h}$, day 15	H-TZ[a] Mean (STDV) 0.915 mg/L (0.396) 1.427 mg/L (0.449) $C_{min\ 12h}$, day 7 H-ITZ[a] Mean (STDV) 1.275 mg/L (0.322) 1.964 mg/L (0.562) $C_{min\ 12h}$, day 7 H-ITZ[a] Mean(STDV) 1.536 mg/L (0.334) 1.919 mg/L (0.535) C_{ssmin}	H-ITZ Mean (STDV) 14 days (8) 11 days (5) T_{Css}	H-ITZ[a] Mean (STDV) 28.488 mg*h/L (5.59) 36.840 mg*h/L (10.1) $AUC_{min/d}$	NR	NR	NR	

Table 6 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters							References
						C_{max}	C	T_{max}	AUC	$T_{1/2}$	CL	V_d	
HIV-infected patients aged 5–18 years with oropharyngeal candidiasis	2.5 mg/kg every 12 or 24 h	PO(oral solution)	NR	26	FD	ITZ[a] Mean (STDV) 0.420 mg/L (0.06) C_{max}	NR	ITZ Mean (STDV) 2.35 h (0.37) T_{max}	ITZ[a] 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]
						H-ITZ[a] Mean (STDV) 0.319 mg/L (0.04) C_{max}	NR	H-ITZ Mean(STDV) 7.14 h (1.69) T_{max}	H-ITZ[a] 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	
					MD QD BID	ITZ[a] Mean (STDV) 0.623 mg/L (0.14) C_{max} Mean (STDV) 1.340 mg/L (0.22) C_{max}	ITZ[a] Mean (STDV) 0.192 mg/L (0.06) C_{min} Mean (STDV) 0.782 mg/L (0.19) C_{min}	ITZ Mean(STDV) 1.9 h (0.3) Mean(STDV) 1.8 h (0.3) T_{max}	ITZ[a] Mean (STDV) 7.05 mg*h/L (2.06) AUC_{0-tau} 7.05 mg*h/L (2.06) AUC_{0-24} Mean (STDV) 11.52 mg*h/L (2.19) AUC_{0-tau} 23.04 mg*h/L (4.39) AUC_{0-24}	ITZ Mean (STDV) 58.9 h (13.1) $T_{1/2}$ Mean (STDV) 104.2 h (28.3) $T_{1/2}$	ITZ Mean (STDV) 0.601 L/h/kg (0.26) Mean (STDV) 0.073 L/h/kg (0.029)	ITZ Mean (STDV) 15.52 L/kg (4.47) $V_{d,ss}$ Mean (STDV) 5.11 L/kg (1.28) $V_{d,ss}$	
					MD QD BID	H-ITZ[a] Mean (STDV) 0.552 mg/L (0.08) C_{max} Mean (STDV) 1.170 mg/L (0.18) C_{max}	H-ITZ[a] Mean (STDV) 0.383 mg/L (0.10) C_{min} Mean (STDV) 0.997 mg/L (0.15) C_{min}	H-ITZ Mean(STDV) 5.9 h (1.5) Mean(STDV) 14.7 h (6.9) T_{max}	H-ITZ[a] Mean (STDV) 11.18 mg*h/L (2.82) AUC_{0-tau} 11.18 mg*h/L (2.82) AUC_{0-24} Mean (STDV) 11.89 mg*h/L (2.06) AUC_{0-tau} 23.75 mg*h/L (4.11) AUC_{0-24}	H-ITZ Mean (STDV) 55.6 h (21.3) $T_{1/2}$ Mean (STDV) 168.8 h (81.3) $T_{1/2}$	H-ITZ Mean (STDV) 0.160 L/h/kg (0.05) Mean (STDV) 0.047 L/h/kg (0.01)	NR	

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

[a]Values recalculated/adjusted from the original paper to create uniformity of units

[b]Error not mentioned

Table 7 Population pharmacokinetic estimates of itraconazole

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters											References
						AUC	$T_{1/2}$	T_{lag}	CL	*V*1	*Q*1	*V*2	*Q*2	*V*3	K_a	*F*	
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[a,d] Estimated value 16.9 L/h	ITZ[a,d] Estimated value 63.8 L	ITZ[a,d] Estimated value 30.2 L/h	ITZ[a,d] Estimated value 134 L	ITZ[a,d] Estimated value 9.57 L/h	ITZ[a,d] Estimated value 88.1 L	NR	NR	[39]
Pediatric patients with CF and BMT patients aged 0.4–18 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 (including 5 adults)	MD	NR	NR	Mean (RSE%) 19.1 min (3.3)	ITZ[b] Mean (RSE%) 35.5 L/h (13.8) H-ITZ Mean (RSE%) 10.6 L/h (14.1)	ITZ[b] Mean (RSE%) 627.0 L (27.3) H-ITZ Mean (RSE%) 5.29 L (4.1)	NR NR	NR NR	NR NR	NR NR	Mean (RSE%) 0.09 1/h (21.7) Capsule Mean (RSE%) 0.96 1/h (67.4) solution	Mean (RSE%) 0.55 (12.7) $F_{relative}$[c]	[45]

AUC area under the curve, *BMT* bone marrow transplantation, *CF* cystic fibrosis, *CL* clearance, *F* bioavailability, *FD* first dose, *H-ITZ* hydroxy-itraconazole, *IFD* invasive fungal disease, *ITZ* itraconazole, K_a rate of oral bioavailability, *MD* multiple dose, *N* number of patients, *NR* not reported, *Q1* intercompartmental clearance (compartments 1–2), *Q2* intercompartmental clearance (compartments 1–3), *RSE* relative standard error, *SD* single dose, *STDV* standard deviation, $T_{1/2}$ elimination half-life, T_{lag} lag time, *V1* volume of distribution (central compartment 1), *V2* volume of distribution (peripheral compartment 2), *V3* volume of distribution (peripheral compartment 3)

[a]Values scaled to a body weight of 30 kg

[b]Values scaled to a body weight of 70 kg

[c]Relative bioavailability of capsules compared to solution

[d]Error was not reported

Table 8 Pharmacokinetic models of itraconazole

Population	Subjects, *N*	Samples, *N*	Program	Covariates tested	Compartments	PO/IV	Covariates in final model								References
							CL	V1	*Q*1	*V*2	*Q*2	*V*3	*F*	K_a	
Children at risk for IFD aged 6 months to 16 years	33	NR	NON-MEM	WT	3, with first-order elimination	IV	WT normalized to 30 kg	WT normalized to 30 kg	WT normalized to 30 kg	WT normalized to 30 kg	WT normalized to 30 kg	WT normalized to 30 kg	NR	NR	[39][a]
Pediatric patients with CF and BMT aged 0.4–18 years (including 5 adults aged 19–30 years)	49 (29 CF of which 5 adults and 20 BMT)	227	NON-MEM	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)	ITZ Allometrically scaled WT normalized to 70 kg[b]	ITZ Allometrically scaled WT normalized to 70 kg[b]	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	

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

[a]WT is included as covariate on itraconazole parameters, however the covariate equation was not reported

[b]Values of exponents used for allometric scaling are not reported

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. Clearance 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.

5.3 Summary of Findings and Recommendations

Pharmacokinetic studies of itraconazole are limited in pediatric patient 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 with 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 optimize 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 warrant further investigation. Pediatric 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 aged < 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.

6 Voriconazole

Voriconazole was both European Medicines Agency 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 pediatric patients aged ≥ 2 years are treatment of invasive aspergillosis, candidemia in patients without neutropenia, esophageal 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 pediatric ESCMID-ECMM guideline for invasive aspergillosis, and the pediatric ESCMID invasive candidiasis guideline provide dose recommendations for pediatric patients aged ≥ 2 years. For prophylaxis and treatment of both invasive aspergillosis and candidiasis, a loading dose of 9 mg/kg twice daily on day 1, followed by 8 mg/kg twice daily intravenously or 9 mg/kg (maximum 350 mg) twice daily for the oral formulations in pediatric 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 pediatric 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].

6.1 Non-Compartmental Analysis of Voriconazole PK in Pediatric Patients

There are no NCA of voriconazole PK available in neonates and infants. Five NCA are available in pediatric patients aged 2–17 years. A detailed overview of the dosing regimens and voriconazole pharmacokinetic results is given in Table 9. Patients with hematological and non-hematological 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 (maximum 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 6 to 9 mg/kg twice daily [50–54].

Overall, only one study reported the *F* of voriconazole from 43.6 to 90.0% [52]. This *F* in pediatric 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 with 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 pediatric 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 pediatric 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 of 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 pediatric 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 (< 50 kg) had a higher exposure compared with patients aged 2–11 years and that patients aged 12–14 years (≥ 50 kg) had a lower exposure compared with patients aged < 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 also have played a role in the differences in voriconazole PK [54]. Two studies showed an overall higher exposure of voriconazole compared with the other studies [53, 54]. This higher exposure might be explained by the higher dosing regimens used.

6.2 Population Pharmacokinetic Analysis of Voriconazole in Pediatric Patients

There are no population pharmacokinetic analyses of voriconazole available in neonates. One study included infants, but did not describe the pharmacokinetic results for this population separately [55]. In total, nine studies were performed in pediatric patients aged 0.8–21 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 hematological or non-hematological 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- and time-dependent voriconazole elimination [57, 59]. The PK models and covariates tested are summarized in Table 11.

Seven studies in pediatric patients administered either an oral solution or tablets of voriconazole in which the *F* was from 44.6 to 85% [55–60, 62]. The *F* found in these studies was also lower compared with the *F* of 96% reported in adults [5]. Similar to findings in the NCA, it remains unclear if the influence of food was attributed to this difference. The K_a had a range of 0.43–1.53 h^{-1} [55–60, 62]. Allometrically scaled bodyweight with fixed exponents [56–60, 63] was added on either CL [57, 59, 63], V_d [57–60, 63], and/or maximum rate of enzyme activity [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 the CYP2C19 genotype [61, 62], alanine aminotransferase (ALT) [61, 62], and alkaline phosphatase on CL. In these studies, the CYP2C19 genotype in the combined group of heterozygous extensive/poor CYP2C19 metabolizers [61, 62], ALT [61, 62], and alkaline phosphatase [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].

6.3 Physiologically Based PK of Voriconazole

One physiologically based pharmacokinetic model was developed for voriconazole in children. The physiologically based pharmacokinetic-derived values from the initial oral model showed an overprediction for *F*, area under the curve (AUC), and maximum serum concentration 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].

6.4 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

Table 9 Non-compartmental analyses of voriconazole

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters								References
						C_{max}	C_{min}	T_{max}	AUC	$T_{1/2}$	CL	V_d	*F*	
Hemato-oncology or HSCT pediatric patients aged 2 to < 12 years	7 mg/kg IV every 12 h for 7 days followed by 200 mg PO every 12 h for 6.5 days	IV and PO	Median (range) 18.9 kg (10.8–54.5)	40	FD/MD Day 1 IV Day 7 IV Day 7 PO	Median (range) 1.99 µg/mL (0.90–6.68) C_{max} 4.49 µg/mL (1.48–15.4) $C_{max\ SS}$ 4.11 µg/mL (0.51–18.0) $C_{max\ SS}$	Median (range) NR 0.61 µg/mL (0.06–10.9) $C_{min\ SS}$ 0.49 µg/mL (0.04–128) $C_{min\ SS}$	Median (range) 2.30 h (0.72–4.08) 2.30 h (1.00–4.07) $T_{max\ SS}$ 1.07 h (0.73–8.03) $T_{max\ SS}$	Median (range) 7.00 µg*h/mL (2.43–36.6) AUC_{0-12} 21.8 µg*h/mL (5.02–162) AUC_{0-12SS} 20.1 µg*h/mL (1.70–203) AUC_{0-12SS}	NR	NR	NR	NR	[51]
Hemato-oncology pediatric patients aged 2 to < 12 years	Group A: 7 mg/kg IV every 12 h Group B: 6 mg/kg IV every 12 h, followed by a maintenance dose of 5 mg/kg IV every 12 h	IV	Mean (range) 24.2 kg (13–41)	12 (9 in group A and 3 in group B)	MD Day 3 Group A Group B	Geometric mean (range) 11.4 µg/mL (2.9–19.2) 5.8 µg/mL (2.4–17.2)	Geometric mean (range) 4.1 µg/mL (0.4–8.9) C_{avg} 2.2 µg/mL (1.1–3.5) C_{avg}	Geometric mean (range) 1.1 h (1.0–1.1) 1.0 h (1.0–1.1)	Geometric mean (range) 49.3 µg*h/mL (4.7–106.6) AUC_{0-12} 26.1 µg*h/mL (12.6–41.5) AUC_{0-12}	Geometric mean (range) 10.9 h (3.1–29.2) 7.7 h (4.2–14.6)	Geometric mean (range) 141.9 mL/h/kg (65.7–1483.1) CL_{SS} 192.1 mL/h/kg (120.5–396.8) CL_{SS}	Geometric mean (range) 1852 mL/kg (953–3311) V_{SS} 1796 mL/kg (902–2871) V_{SS}	NR	[53]

Table 9 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters								References
						C_{max}	C_{min}	T_{max}	AUC	$T_{1/2}$	CL	V_d	*F*	
Hemato-oncology, BMT and HSCT pediatric patients aged 2 to < 12 years	Cohort 1 Day 1: 6 mg/kg IV every 12 h; days 2–4: 4 mg/kg IV every 12 h; days 5–8: 6 mg/kg IV every 12 h.; days 9–11: 4 mg/kg PO every 12 h; from day 12: 4 mg/kg PO every 12 h Cohort 2 Day 1: 6 mg/kg IV every 12 h; days 2–4: 6 mg/kg IV every 12 h; days 5–8: 8 mg/kg IV every 12 h; days 9–11: 6 mg/kg PO every 12 h; from day 12: 6 mg/kg PO every 12 h	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 2–5 years 4 mg/kg IV 6 mg/kg IV 4 mg/kg PO 6–11years 4 mg/kg IV 6 mg/kg IV 4 mg/kg PO 2–11 years 4 mg/kg IV 6 mg/kg IV 4 mg/kg PO	Geometric mean (CV%)[a] 3.352 µg/mL (71) 4.690 µg/mL (111) 0.956 µg/mL (85) 3.067 µg/mL (64) 4.009 µg/mL (88) 1.555 µg/mL (54) 3.212 µg/mL (67) 4.353 µg/mL (103) 1.178 µg/mL (70)	NR	Arithmic mean (CV%) 1.36 h (15) 1.97 h (0) 1.50 h (144) 1.36 h (16) 1.97 h (0) 1.33 h (82) 1.36 h (15) 1.97 h (0) 1.43 h (122)	Geometric mean (CV%)[a] 11.722 µg*h/mL (76) 21.931 µg*h/mL (125) 3.788 µg*h/mL (78) AUC_{tau} 11.954 µg*h/mL (78) 24.047 µg*h/mL (129) 7.346 µg*h/mL (60) AUC_{tau} 11.827 µg*h/mL (75) 22.914 µg*h/mL (125) 5.184 µg*h/mL (71) AUC_{tau}	NR	NR	NR	Arithmic mean (CV%) NR NR 43.6 % (88) NR NR 90.0% (86) NR NR 66.0 % (97)	[52]
					Cohort 2 MD 2–5 years 6 mg/kg IV 8 mg/kg IV 6 mg/kg PO 6-11 years 6 mg/kg IV 8 mg/kg IV 6 mg/kg PO 2–11 years 6 mg/kg IV 8 mg/kg IV 6 mg/kg PO	Geometric mean (CV%)[a] 4.609 µg/mL (93) 4.804 µg/mL (83) 1.433 µg/mL (66) 3.986 µg/mL (67) 6.924 µg/mL (123) 2.213 µg/mL (49) 4.286 µg/mL (85) 5.767 µg/mL (121) 1.762 µg/mL (57)	NR	Arithmetic mean (CV%) 1.97 h (0) 2.63 h (0) 1.00 h (58) 2.17 h (30) 3.04 h (22) 1.72 h (98) 2.07 h (22) 2.84 h (18) 1.34 h (93)	Geometric mean (CV%)[a] 18.216 µg*h/mL (87) 25.566 µg*h/mL (81) 6.959 µg*h/mL (104) AUC_{tau} 16.234 µg*h/mL (60) 34.681 µg*h/mL (81) 10.076 µg*h/mL (56) AUC_{tau} 17.249 µg*h/mL (80) 29.776 µg*h/mL (82) 8.373 µg*h/mL (80) AUC_{tau}	NR	NR	NR	Arithmetic mean (CV%) NR NR 63.4 % (88) NR NR 66.7% (53) NR NR 65.1% (70)	

Table 9 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters								References
						C_{max}	C_{min}	T_{max}	AUC	$T_{1/2}$	CL	V_d	*F*	
Immunocompromised hemato-oncology and non-hemato-oncology Japanese pediatric patients aged 2 to < 15 years	2–12 years or 12–15 years (< 50 kg): day 1: 9 mg/kg IV every 12 h; days 2–7: 8 mg/kg IV every 12 h; days 8–14: 9 mg/kg PO every 12 h (maximum 350 mg) 12–5 years (≥ 50 kg): day 1: 6 mg/kg every 12 h IV; days 2–7: 4 mg/kg IV every 12 h; days 8–14: 200 mg PO every 12 h	IV and PO	Mean (range) 30.4 kg (11.5–55.2)	21	MD IV 2–11 years 12–14 years (< 50 kg) 12–14 years (≥ 50 kg) All	Median (range) 8.21 µg/mL (4.62–12.6) $C_{max,ss}$ 7.72 µg/mL (6.24–19.6) $C_{max,ss}$ 3.22 µg/mL (2.32–4.12) $C_{max,ss}$ 7.72 µg/mL (2.32–19.6) $C_{max,ss}$	Median (range) 2.89 µg/mL (0.596–9.36) $C_{min,ss}$ 4.31 µg/mL (3.09–10.4) $C_{min,ss}$ 0.576 µg/mL (0.471–0.680) $C_{min,ss}$ 3.00 µg/mL (0.471–10.4) $C_{min,ss}$	Median (range) 2.96 h (0.950–4.00) 4.00 h (2.92–4.20) 1.34 h (1.00–1.67) 2.96 h (0.950–4.20)	Median (range) 60.2 µg*h/mL (23.0–103) $AUC_{0-12,ss}$ 70.5 µg*h/ml (55.7–177) $AUC_{0-12,ss}$ 17.6 µg*h/mL (14.2–21.0) $AUC_{0-12,ss}$ 59.3 µg*h/mL (14.2–177) $AUC_{0-12,ss}$	NR	NR	NR	NR	[54]
					MD PO 2 to < 12 years 12–14 years (< 50 kg) 12–14 years (≥ 50 kg) All	Median (range) 6.70 µg/mL (3.58–18.3) $C_{max,ss}$ 6.21 µg/mL (6.13–13.0) $C_{max,ss}$ 2.03 µg/mL[b] $C_{max,ss}$ 6.48 µg/mL (2.03–18.3) $C_{max,ss}$	Median (range) 2.06 µg/mL (0.148–12.3) $C_{min,ss}$ 3.00 µg/mL (1.09–6.59) $C_{min,ss}$ 0.306 µg/mL[b] $C_{min,ss}$ 2.06 µg/mL (0.148–12.3) $C_{min,ss}$	Median (range) 1.09 h (0.917–3.78) 1.00 h (0.950–2.03) 1.00 h[b] 1.04 h (0.917–3.78)	Median (range) 45.6 µg*h/mL (12.4–156) $AUC_{0-12,ss}$ 49.4 µg*h/mL (36.3–117) $AUC_{0-12,ss}$ 10.0 µg*h/mL[b] $AUC_{0-12,ss}$ 45.6 µg*h/mL (10.0–156) $AUC_{0-12,ss}$	NR	NR	NR	NR	
Hemato-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 12 h for the next 6 days and were switched to 300 mg PO every 12 h	IV and PO	Median (range) 57.1 kg (30.4–92.2)	26	FD/MD Day 1 IV Day 7 IV Day 7 PO	Median (range) 2.36 µg/mL (0.66–4.02) C_{max} 3.72 µg/mL (1.171–9.99) $C_{max,ss}$ 2.84 µg/mL (0.18–5.88) $C_{max,ss}$	Median (range) NR 1.59 µg/mL (0.08–7.78) $C_{min,ss}$ 1.05 µg/mL (0.04–2.84) $C_{min,ss}$	Median (range) 1.97 h (1.90–2.08) T_{max} 1.30 h (1.17–3.95) $T_{max,ss}$ 2.00 h (0.67–8.10) $T_{max,ss}$	Median (range) 9.51 µg*h/mL (2.52–21.6) AUC_{0-12} 27.9 µg*h/mL (6.24–95.3) $AUC_{0-12,ss}$ 18.7 µg*h/mL (1.17–49.7) $AUC0_{0-12,ss}$	NR	NR	NR	NR	[50]

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

[a]Values recalculated/adjusted from the original paper to create uniformity of units

[b]Values from 1 patient

Table 10 Population pharmacokinetic estimates of voriconazole

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters				
						AUC	T	Tl_{ag}	CL	*V*1
Hemato-oncology patients and patients with other diseases aged 8–15 years	NR	IV and PO	NR	55	MD	NR	NR	NR	NR	WtMedian (95% CI)0.67 L/kg (0.61–0.70)
Immunocompromised children and adolescents aged 2–17 years (also adult data included)	2 to < 12 years IV: day 1: 6 mg/kg every 12 h; days 2–4: 3 mg/kg every 12 h; days 5–8: 4 mg/kg every 12 h 2 to 12 years IV and PO: day 1: 6 mg/kg IV every 12 h; days 2–4: 4 mg/kg IV every 12 h; days 5–8: 6 mg/kg IV every 12 h; days 9–12: 4 mg/kg PO every 12 h Or days 1–4: 6 mg/kg IV every 12 h; days 5–8: 8 mg/kg IV every 12 h; days 9–12: 6 mg/kg PO every 12 h Or days 1–7: 7 mg/kg IV every 12 h; days 8–14 200 mg PO every 12 h. 12 to < 17 years IV and PO: day 1: 6 mg/kg IV every 12 h; days 2–7: 4 mg/kg IV every 12h; days 8–14: 300 mg PO every 12 h Adults: day 1: 6 mg/kg IV every 12 h; days 2–7: 4 mg/kg IV every 12 h; days 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)	$0.949 \cdot (1 + (-0.874 \times (1 - \text{STDY5,adult})))^{c}$	$6.16 \times (\text{WT}/70)^{0.75}$	$79.0 \times \text{WT}/70$

Table 10 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters				
						AUC	T	Tl_{ag}	CL	*V*1
HSCT patients aged 2 to ≤12 years and >12 years[b]	≤12 years: 7 mg/kg every 12h IV >12 years: 6 mg/kg every 12 h for the first 24 h, followed by 4 mg/kg every 12 h thereafter If possible switched to PO with a fixed dose of 200 mg every 12 h 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	Value (RSE%) 228 L/70kg (13.5)
Patients with hematological 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 12 h (Study B), followed by MD PO 4 and 6 mg/kg every 12 h (study C)	IV and PO (suspension)	Median (range) 22.8 kg (10.8–54.9)	82	MD	NR	NR	NR	Value (RSE%) 0.582 L/h/kg (19) CL in EMs Decreased in CL for HEMs/PMs (35.5%)	Value (RSE%) 0.807 L/kg (14)
Immunocompromised Japanese children aged 2 to <15 years	2–12 and 12–15 years (<50 kg): day 1: 9 mg/kg IV every 12 h; day 2-7: 8 mg/kg IV every 12h; days 8–14: 9 mg/kg PO every 12 h (maximum 350 mg) 12–5 years (≥50 kg): day 1; 6 mg/kg every 12h IV; days 2–7: 4 mg/kg IV every 12 h; days 8–14: 200 mg PO every 12 h	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}	$CL = 6.02 \times (WT/70)^{0.75}$	$75.0 \times (WT/70)$
Patients with hematological 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	WtMedian (95% CI) 1.20 L/kg (1.09–1.31) $V_{central}$

Table 10 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters				
						AUC	T	Tl_{ag}	CL	*V*1
Immuno-compromised with hematological and non-hematological 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)	Geometric mean (GRSE%) 0.27 L/kg (188) 0.17 L/kg (188)
Immuno-compromised children aged 2–11 years	SD: 3 or 4 mg/kg MD: day 1: loading dose of 6 mg/kg every 12 h; days 2–4: 3 mg/kg every 12 h; days 4–8: 4 mg/kg every 12 h	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%)[e] 0.40 L/h/kg (14) CL in EMs Decreased CL in HEMs/PMs of 46%.	Value (RSE%)[e] 0.80 L/kg (20)
Patients undergoing HSCT aged < 2 to 21 years		IV	NR	59	MD	NR	NR	NR	$4.60 \times (WT/70)^{0.75} \times [(Age^{Hill\ coef})/(Age^{Hill\ coef} + TM^{Hill\ coef})]$ $CL_{voriconazole}$ $3.62 \times (WT/70)^{0.75}$ Apparent $CL_{metabolite}$	$52.4 \times (WT/70)^{1}$

Pharmacokinetic parameters									References
*Q*1	*V*2	*Q*2	*V*3	*K*	*F*	V_{max}	$V_{max,inh}$	K_m	
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]
$15.5 \times (WT/70)^{0.75} \times (1 + 0.637 \times (1 - STDY5,adult))$[c]	$103 \times WT/70$	NR	NR	$(1.19 \times (1 - 0.615 \cdot STDY4,adol) \times (1 - STDY5,adult) + 0.0912 \times STDY5,adult)$[c] K_a	Value (RSE%) 0.585(13) logit(F)	$114 \times (WT/70)^{0.75} \times (1 + (-0.382 \times STDY1,ped))$[c] $V_{max,\ 1h}$ Concentration and time-dependent V_{max}	$1.50 + (-0.390 \times (AGE < 12))$[d] logit($V_{max,inh}$)	$1.15 \times (1 + (-0.382 \times STDY1,ped))$[c]	[57]

Table 10 (continued)

Pharmacokinetic parameters									References
*Q*1	*V*2	*Q*2	*V*3	*K*	*F*	V_{max}	$V_{max,inh}$	K_m	
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]
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%)[a] 3.030 mg/L (45)	[62]
$24.6 \times (WT/70)^{0.75}$	$101 \times (WT/70)$	NR	NR	Estimate (RSE%) 1.38 1/h (14) k_a	Estimate (RSE%) 0.597 (13) logit(F)	$118 \times (WT/70)^{0.75}$ $V_{max,\ 1h}$ Concentration and time-dependent V_{max}	Estimate (RSE%) 2.61 (19) logit($V_{max,inh}$)	Estimate (RSE%)[a] 0.922 mg/L (30)	[59][b]
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%) 0.43 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 L/h (164) K_a 0.43 L/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%)[e] 0.64 L/h/kg (15)	Value (RSE%)[e] 1.7 L/kg (7.5%)	NR	NR	NR	NR	NR		NR	[61]
$13.3 \times (WT/70)^{0.75}$	$86.7 \times (WT/70)^{1}$	NR	NR	NR	NR	$36.2 \times (WT/70)^{0.75}$	NR	Estimate (RSE%) 1.57 mg/L (34.8)	[63]

A_{lag} absorption lag time, *AUC* area under the curve, *CF* cystic fibrosis, *CI* confidence interval, *CL* clearance, *CYP* cytochrome P450, *EMs* homozygous extensive CYP2C19 metabolizers, *F* bioavailability, *FD* first dose, *GRSE* geometric relative standard error, *h* hours, *HEMs* heterozygous extensive CYP2C19 metabolizers, *Hill coef* Hill coefficient fixed to 1, *HSCT* hematopoietic stem cell transplantation, *IV* intravenous, K_a rate of oral bioavailability, K_{cp} rate constant from central to peripheral compartment, K_m Michaelis–Menten constant, K_{pc} rate constant from peripheral to central compartment, *MD* multiple dose, *N* total patients, *NR* not reported, *PMs* poor CYP2C19 metabolizers, *PO* 'per os', *Q1* intercompartmental clearance, *Q2* intercompartmental clearance, *RSE* relative standard error, *SD* single dose, T_{50} time at half of the maximum inhibition of V_{max},, $T_{1/2}$ elimination half-life, T_{lag} lag time, *V1* volume of distribution of the central compartment, *V2* volume of distribution of the peripheral compartment, *V3* volume of distribution of the peripheral compartment, V_{max} maximum rate of enzyme activity, $V_{max,\ inh}$ maximum fraction of the V_{max} inhibition, *WtMedian* weighted median

[a]Values recalculated/adjusted from the original paper to create uniformity of units

[b]Based on priors

[c]Values for STDY1,ped; STDY4,adol and STDY5,adult indicate variables of 0 or 1, dependent on the study group

[d]$V_{max,\ inh}$ =100% if CYP2C19 is equal to HEM or PM

[e]Estimates for a typical model patient, but the typical model patient is not defined

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 pediatric 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 pediatric 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.

Noncompartmental analyses report that patients aged < 12 years seem to have a higher CL and V_d compared with 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 pediatric 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.

7 Posaconazole

In 2005, posaconazole received European Medicines Agency 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 pediatric patients aged > 13 years for prophylaxis and treatment of invasive aspergillosis and invasive candidiasis [8], but in Europe posaconazole is not approved in pediatric patients aged < 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 pediatric 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 using 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-resistant tablets show saturable absorption, but for the gastro-resistant tablets this was only seen for daily doses above 800 mg of posaconazole [67, 68]. Absorption of the marketed posaconazole suspension is significantly influenced by food intake and administration in a 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 because of 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, and 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 enzymes, and particularly uridine diphosphate glucuronosyltransferase 1A4 (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 the urine and feces accounted for about 17% of the radioactive-labeled posaconazole [8, 66]. Mean CL is 7.3 L/h [8].

7.1 Non-Compartmental Analysis of Posaconazole PK in Pediatric Patients

Currently, there are no NCA studies 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 hematological and non-hematological malignancies or

Table 11 Pharmacokinetic models of voriconazole

Population	Subjects, *N*	Samples, *N*	Program	Covariates tested	Compartments	PO/IV	Covariates in final model										References
							CL	*V*1	*Q*1	V2	*Q*2	*V*3	*K*	V_{max}	$V_{max,inh}$	*F*	
Children and adolescent cancer patients aged 8–15 years	55	158	Pmetrics	Ethnic group, age, sex, WT, hepatic dysfunction	2, with first-order absorption and nonlinear elimination	PO and IV	NR	NR	NR	NR	NR	NR	NR	Allometrically scaled bodyweight with a fixed exponent of 0.75	NR	NR	[56]
Immunocompromised children and adolescents aged 2–17 years.	112 children 26 adolescents 35 adults	2022 554 760	NON-MEM	Age, WT, CYP2C19 genotyping status, 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	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]
Immunocompromised children aged 2 to ≤ 12 years and > 12 years.	23	187	NON-MEM	Age, sex, WT, CRP, bilirubin, AST, ALT, GGT, AP, creatinine.	2, with first-order absorption and nonlinear elimination	PO and IV	NR	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]
Immunocompromised children aged 2 to < 12 years	82	1274	NON-MEM	Age, sex, WT, HT, ethnic origin, serum creatinine, AST, ALT, AP, GGT, ALB, total bilirubin, total protein levels, CYP2C19, CYP2C9 and CYP3A4 inhibitors, CYP450 inducers, leukemia, BMT, aplastic anemia, lymphoma, or other, CYP2C19 genotype status, presence of mucositis	2, with first-order absorption and nonlinear elimination	PO and IV	WT, CYP2C19 genotype, ALT(loglinear)	WT	WT	WT	NR	NR	NR	NR	NR	NR	[62]
Immunocompromised Japanese children aged 2 to < 15 years	21	276	NON-MEM	WT, age, sex, 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 normalized to 70 kg	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	[59]

Table 11 (continued)

Population	Subjects, *N*	Samples, *N*	Program	Covariates tested	Compartments	PO/IV	Covariates in final model									References
							CL	*V*1	*Q*1	V2	*Q*2	*V*3	*K*	V_{max}	$V_{max,inh}$	*F*	
Patients with hematological 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	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]
Immunocompromised children aged 0.8–20.5 years	40	108	NPAG	WT, age, sex, creatinine clearance, ALT, AP	2, with delayed absorption and nonlinear elimination	PO and IV	WT, age	WT, age	WT	WT, age	NR	NR	NR	NR	NR	NR	[55]
Immunocompromised children aged 2–11 years	35	355	NONMEM	WT, CYP2C19 genotype, ALT, AP	2, with linear elimination	IV	WT, CYP2C19 genotype, ALT (loglinear) and AP (loglinear)	WT	WT	WT	NR	NR	NR	NR	NR	NR	[61]
Patients undergoing HSCT aged < 2 to 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 normalized to 70 kg for both voriconazole and metabolite; maturation factor for voriconazole	Allometrically scaled bodyweight with a fixed exponent of 1 and normalized to 70 kg	Allometrically scaled bodyweight with a fixed exponent of 0.75 and normalized to 70 kg	Allometrically scaled bodyweight with a fixed exponent of 1 and normalized to 70 kg	NR	NR	NR	Allometrically scaled bodyweight with a fixed exponent of 0.75 and normalized to 70 kg	NR	NR	[63]

ALB albumin, *ALT* alanine aminotransferase, *AP* alkaline phosphatase, *AST* aspartate aminotransferase, *CF* cystic fibrosis, *CL* clearance, *CRP* C-reactive protein, *CYP* cytochrome P450, *F* bioavailability, *GGT* gamma-glutamyl transferase, *HSCT* hematopoietic stem cell transplantation, *HT* height, *IV* intravenous, *K* rate constant, *MD* multiple dose, *N* total patients or samples, *NONMEM* nonlinear mixed effect modeling, *NPAG* non-parametric adaptive grid modeling, *NR* not reported, *PO* 'per os', *POS* powder for oral suspension, *Q1* intercompartmental clearance, *Q2* intercompartmental clearance, *SD* single dose, *V1* volume of distribution of the central compartment, *V2* volume of distribution of the peripheral compartment, *V3* volume of distribution of the peripheral compartment, V_{max} maximum rate of enzyme activity, *WT* weight

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 an 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 to 9 mg/kg or increasing the dosing frequency of the marketed suspension from two times daily to three times daily did not increase the exposure of posaconazole. This suggests saturable absorption in pediatric patients, which is also seen in adults. The authors suggested that children aged >7 years showed higher exposures compared with 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 were 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 with 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 with older patients in all dosing groups [74, 76]. Furthermore, the exposure after oral PFS administration was lower compared with intravenously administered posaconazole. As suggested by the authors, there seems to be no bioequivalence between the intravenous and new PFS formulations in pediatric patients [76].

7.2 Population Pharmacokinetic Analysis of Posaconazole in Pediatric 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 0.5–18 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 the relative *F* of the marketed suspension was seen in patients with diarrhea and a 42% decrease in patients using proton pump inhibitors. As only the oral marketed formulations were used, V_d/F and apparent CL were determined. Allometrically scaled bodyweight normalized to 70 kg was added as covariate on posaconazole V_d/F and apparent CL [77].

7.3 Summary of Findings and Recommendations

Pediatric pharmacokinetic data of posaconazole are very limited, and future research is particularly needed to explain the 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-resistant tablets are the preferred formulation, but there are no pharmacokinetic data of this formulation available in pediatric 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 the 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 pediatric patients. Exposures after administration of the not yet marketed posaconazole PFS were lower compared with 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 pediatric NCA only administered the suspension of posaconazole as an 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 with 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 PK 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 its unbound drug concentrations on posaconazole PK.

8 Isavuconazole

The relatively new triazole isavuconazole is not licensed for pediatric patients. The European Medicines Agency 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 pediatric patients and the international guideline does not provide recommendations for dosing of isavuconazole in pediatric patients [1]. Dose finding trials have been completed or are ongoing, thus 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 the 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 uridine diphosphate glucuronosyltransferase (Table 1) [7].

To our current knowledge, there is only one pediatric study of isavuconazole available in the public domain outside of conference abstracts and case reports. This retrospective study included 29 patients with a hematological malignancy aged 3–18 years. In six patients, an 8-point sample curve was obtained over 12 h. The demographics and dosing regimens are not reported for these six patients separately. The median AUC_{0-12h} (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.

8.1 Summary of Findings and Recommendations

Data on the PK of isavuconazole are urgently needed in pediatric patients including population pediatric PK data. Specifically for pediatric patients, information on *F* including information on dosing via a nasogastric tube are needed as well as information on bioequivalence after the 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.

9 Conclusions

This review shows that the PK of fluconazole is extensively studied in the neonatal population and the PK of voriconazole is extensively studied in children and adolescents. Isavuconazole, itraconazole, and posaconazole are studied to a limited extent. 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 the 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 pediatric 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

Table 12 Non-compartmental analyses of posaconazole

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters								References
						C_{max}	C	T_{max}	AUC	$T_{1/2}$	CL	V_d	F	
Pediatric patients with hematological, non-hematological malignancies, or HSCT and neutropenia aged 3 months to < 18 years	7 to < 18 years; 6 mg/kg PO every 12 h or 9 mg/kg PO every 12 h or 6 mg/kg every 8 h PO for 7–28 days 2 to < 7 years; 6 mg/kg every 12 h PO or 9 mg/kg every 12 h PO or 6 mg/kg every 12 h PO for 7–28 days 3 months to < 2 years 6 mg/kg every 12h PO or via enteral tube for 7–28 days	PO (suspension)	Median 29.8 kg	136	Day 1 FD 3 mo to < 2 years 6 mg/kg BID PO 2 to < 7 years 6 mg/kg (BID PO) 9 mg/kg (BID PO) 6 mg/kg (TID PO) 7 to < 18 years 6 mg/kg (BID PO) 9 mg/kg (BID PO) 6 mg/kg (TID PO)	Value[a] 103 ng/mL[b] 196 ng/mL (93.9) 175 ng/mL (70.5) 109 ng/mL (61.3) 156 ng/mL (78.1) 162 ng/mL (86.7) 93.2 ng/mL (60.8)	Arithmetic mean (%CV, STDV) 68.5 ng/mL[b] 122 ng/mL (83.1, 101) 112 ng/mL (77.6, 86.9) 68.4 ng/mL (59.2, 40.4) C_{avg} 107 ng/mL (86.5, 92.5) 113 ng/mL (89.1, 100) 57.9 ng/mL (52.2, 30.2) C_{avg}	Median (minimum–maximum) 3.38 h[b] 5.01 h (2.92–11.60) 3.99 h (2.98–11.08) 7.95 h (2.98–8.00) 5.0 h (2.97–12.0) 3.12 h (2.92–8.00) 4.88 h (2.92–8.08)	Value[c] 574 ng*h/mL AUC_{0-12}[b] AUC_{tf} 1300 ng*h/mL (91.4) AUC_{0-12} 1210 ng*h/mL (76.9) AUC_{0-12} 544 ng*h/mL (59.6) AUC_{0-8} AUC_{tf} 1140 ng*h/mL (93.7) AUC_{0-12} 1270 ng*h/mL (98.1) AUC_{0-12} 424 ng*h/mL (49.5) AUC_{0-8} AUC_{tf}	NR	NR	NR	NR	[74]
					Day 7 MD 3 mo to < 2 years 6 mg/kg BID PO 2 to < 7 years 6 mg/kg BID PO 9 mg/kg BID PO 6 mg/kg TID PO 7 to < 18 years 6 mg/kg BID PO 9 mg/kg BID PO 6 mg/kg TID PO	Value[a] 520 ng/m[b] 726 ng/mL (125.5) 581 ng/mL (61.0) 705 ng/mL (60.9) 1200 ng/mL (75.5) 1390 ng/mL (111.4) 1230 ng/mL (64.2)	Arithmetic mean (%CV, STDV) 453 ng/m[b] C_{avg} 604 ng/mL (129.0, 779) 485 ng/mL (63.0, 306) 620 ng/mL (66.2, 411) C_{avg} 1050 ng/mL (76.2, 789) 1240 ng/mL (113.4, 1400) 1150 ng/mL (65.4, 750) C_{avg}	Median (minimum–maximum) 0.00 h[b] 4.13 h (0.0–11.17) 3.00 h (0.0–8.08) 3.00 h (0.0–5.08) 4.58 h (0–7.75) 4.03 h (0.0–28.5) 2.63 h (0.00–7.62)	Value[c] 3590 ng*h/mL AUC_{0-12}[b] AUC_{tf} 6770 ng*h/mL (138.9) AUC_{0-12} 5350 ng*h/mL (62.0) AUC_{0-12} 4920 ng*h/mL (67.1) AUC_{0-8} AUC_{tf} 11800 ng*h/mL (75.4) AUC_{0-12} 13500 ng*h/mL (115.8) AUC_{0-12} 8310 ng*h/mL (74.9) AUC_{0-8} AUC_{tf}	NR	NR	NR	NR	
Children with a hematological malignancies aged 2–13 years	120 mg/m^2 every 8 h	PO (suspension)	Mean (STDV) 19.9 kg (6.1)	14	MD	Mean (STDV)[a] 960 ng/mL (630)	Mean (STDV)[a] 860 ng/mL (580) C_{avg}	NR	Mean (STDV)[a] 20500 ng*h/mL (14000) AUC_{0-24}	NR	Median (IQR)[a] 15.9 L/h (9.95–27.86) CL/F	NR	NR	[75]

Table 12 (continued)

Population	Dose	Formulation	Weight	*N*	SD, FD, or MD	Pharmacokinetic parameters								References
						C_{max}	C	T_{max}	AUC	$T_{1/2}$	CL	V_d	F	
Hematology and oncology patients with documented or expected neutropenia aged 2–17 years	3.5, 4.5, or 6.0 mg/kg IV every 12 h on day 1, followed by 3.5, 4.5, or 6.0 mg/kg (maximum 300 mg) once daily at days 2–10 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) 3.5 mg/kg (PFS) 4.5 mg/kg (PFS) 6.0 mg/kg (PFS)	Geometric mean (%GCV) 1590 ng/mL (43.1) 2320 ng/mL (39.8) 3060 ng/mL (54.1) 884 ng/mL (44.4) 1550 ng/mL (40.8) 1510 ng/mL (43.4)	Geometric mean (%GCV) 743 (55.0) 1070 (30.0) 1300 (48.9) C_{avg} 510 (36.0) 901 (64.5) 960 (47.3) C_{avg}	Median (minimum–maximum) 1.78 h (1.67–5.53) 1.78 h (1.42–5.90) 1.75 h (1.57–1.83) 3.83 h (1.92–4.25) 3.82 h (1.88–5.92) 4.00 h (2.17–7.92)	Geometric mean (%GCV) 17800 ng*h/mL (55.0) 25600 ng*h/mL (30.0) 31100 ng*h/mL (48.9) AUC_{0-24} 12200 ng*h/mL (36.0) 21600 ng*h/mL (64.5) 23000 ng*h/mL (47.3) AUC_{0-24}	NR	Geometric mean (%GCV) 3.39 L/h (52.8) 2.97 L/h (36.2) 3.27 L/h (49.3) CL 4.97 L/h (29.1) 3.49 L/h (59.1) 4.60 L/h (35.2) CL/F	NR	NR	[76]
					7–17 years MD 3.5 mg/kg (IV) 4.5 mg/kg (IV) 6.0 mg/kg (IV) 3.5 mg/kg (PFS) 4.5 mg/kg (PFS) 6.0 mg/kg (PFS)	Geometric mean (%GCV) 2450 ng/mL (72.7) 2310 ng/mL (40.3) 3340 ng/mL (39.4) 1340 ng/mL (30.8) 1670 ng/mL (28.5) 1370 ng/mL (178.5)	Geometric mean (%GCV) 1140 ng/mL (49.7) 1240 ng/mL (42.9) 1930 ng/mL (41.5) C_{avg} 861 ng/mL (33.8) 1200 ng/mL (33.7) 1040 ng/mL (184.3) C_{avg}	Median (minimum–maximum) 1.77 h (0–3.5) 1.75 h (1.52–1.80) 1.77 h (1.33–6.00) 2.20 h (1.92–6.03) 6.14 h (1.98–7.98) 2.78 h (0–4.00)	Geometric mean (%GCV) 27300 ng*h/mL (49.7) 29800 ng*h/mL (42.9) 44200 ng*h/mL (41.5) AUC_{0-24} 20700 ng*h/mL (33.8) 28700 ng*h/mL (33.7) 25000 ng*h/mL (184.3) AUC_{0-24}	NR	Geometric mean (%GCV) 6.64 L/h (38.6) 6.69 L/h (37.3) 4.76 L/h (55.7) CL 7.67 L/h (39.9) 7.84 L/h (49.4) 8.39 L/h (190.3) CL/F	NR	NR	

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

[a]Values recalculated/adjusted from original paper to create uniformity of units

[b]Values from one patient

[c]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	Pharmacokinetic parameters								References
						AUC	$T_{1/2}$	CL	*V*1	K_a	*F*	f_D	f_P	
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	$14.95 \times (WT/70)^{0.75}$ 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]

AUC area under the curve, *CL* clearance, *CL/F* apparent clearance, *F* bioavailability, f_D fractional decrease of the bioavailability in patients with diarrhea (suspension), *FD* first dose, f_P fractional decrease of the bioavailability in patients using proton pump inhibitors (suspension), K_a rate of oral bioavailability, *MD* multiple dose, *N* total patients, *NR* not reported, *PO* 'per os', *RSE* relative standard error, *SD* single dose, $T_{1/2}$ elimination half-life, V_d volume of distribution, *V/F* apparent volume of distribution

Table 14 Pharmacokinetic models of posaconazole

Population	Subjects, *N*	Samples, *N*	Program	Covariates tested	Compartments	PO/IV	Covariates in final model				References
							CL	V	K_a	*F*	
Immunocompromised children aged 5 months to 18 years	117	338	NONMEM	Diarrhea, treatment/prophylaxis, macrolides, echinocandins, terbinafine, ciclosporin, tacrolimus, mycophenolate, rifamycins, carbamazepine, phenytoin, histamine H_2-receptor antagonists, proton pump inhibitors, or valaciclovir on bioavailability Macrolides, echinocandins, ciclosporin, tacrolimus, mycophenolate, rifampicin, carbamazepine, phenytoin, or valaciclovir on CL WT, sigmoidal maturation function based on PMA	1	PO	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	Diarrhea, concurrent proton pump inhibitor administration	[77]

CL clearance, *F* bioavailability, *IV* intravenously, K_a rate of oral bioavailability, *N* total, *PMA* postmenstrual age, *PO* 'per os', *V* volume of distribution

should warrant further exploration. Better understanding of the PK is necessary for optimal clinical care and remaining knowledge gaps will need to be clarified.

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