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Review

Clinical pharmacokinetics of voriconazole

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Abstract

This review presents the published clinical pharmacokinetic data for the antifungal agent voriconazole. Aspects regarding absorption, tissue distribution, elimination and kinetic interactions are also discussed.

Keywords: Voriconazole; Pharmacokinetics; Drug–drug interaction

1. Introduction

Voriconazole (formerly known as UK-109,496) is a recent systemic antifungal agent belonging to the azoles chemical family. Currently, there are five classes of systemic antifungals in clinical practice, the polyenes (amphotericin B), the alkylamines/thiocarbamates (terbinafine), the fluoropyrimidines (fluorocytosine), the azoles and the echinocandins (caspofungin). Apart from ketoconazole, all commonly used systemic azoles are triazoles (three nitrogens in the 5-membered azole ring) and they currently include fluconazole, itraconazole and voriconazole. In Europe, voriconazole is approved for the treatment of adult and paediatric patients with invasive aspergillosis, those with fluconazole-resistant invasive *Candida* infections, non-neutropenic patients with candidaemia and those with emerging infections caused by *Scedosporium* spp. and *Fusarium* spp. This review summarises the published pharmacokinetic data for voriconazole in humans.

2. Pharmacological properties

Voriconazole acts as an enzyme inhibitor blocking the synthesis of ergosterol, a constituent of fungal membranes, and thereby the growth of the microorganism. As with other triazoles (fluconazole, itraconazole), voriconazole binds the active site of the P450-dependent enzyme lanosterol 14α-demethylase (CYP51 or Erg11p) and ligates the iron heme cofactor through a nitrogen atom [1,2]. This inhibition leads to depletion of ergosterol and accumulation of 14α-methyl sterols such as lanosterol, affecting the integrity and function of the fungal membrane [3]. The IC_{50} values (the concentration leading to a 50% decrease in ergosterol synthesis in fungi extracts) for voriconazole are ca. 2 μg/L for *Candida albicans* and 20 μg/L for *Candida krusei*. In comparison, fluconazole IC_{50} values are 10 μg/L for *C. albicans* and 230 μg/L for *C. krusei* (intrinsically resistant to fluconazole). With regard to these two microorganisms, voriconazole is considered to be a more potent inhibitor of CYP51 than fluconazole. Voriconazole is a broad-spectrum antifungal showing in vitro activity against *Candida* spp. including fluconazole-resistant *C. albicans* and *C. krusei*, *Aspergillus* spp. including itraconazole- and amphotericin B-resistant *Aspergillus fumigatus*, and emerging pathogens such as *Scedosporium* spp. and *Fusarium* spp. [4].

3. Drug formulation and administration

Voriconazole is administered by the intravenous (i.v.) and oral routes. It is formulated as lyophilised powder for solution for i.v. infusion, as well as tablets and powder for suspension for oral administration. In adults, the i.v. dosage is adapted on a weight basis, although there are no published

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pharmacological studies to support this (see below). Voriconazole is administered at 6 mg/kg once every 12 h for the first day (loading dose), then at 4 mg/kg once every 12 h. The oral regimen is 200 mg or 400 mg once every 12 h for the first day, then 100 mg or 200 mg once every 12 h, depending on the weight (< or >40 kg, respectively). Voriconazole must be taken before or after a meal. In children (2–12 years), voriconazole is administered orally or intravenously at 6 mg/kg once every 12 h for the first day, then at 4 mg/kg once every 12 h.

4. Analytical methodology

Voriconazole (molecular weight 349.3) is a derivative of fluconazole, differing by the addition of a methyl group on the propanolol backbone and by the replacement of a triazole moiety by a fluoropyrimidine ring. To date, several validated assays have been published [5–13]. As an anti-infective agent, voriconazole has been quantitated in plasma by a classical microbiological assay (bioassay) [7,10] and by liquid chromatography with ultraviolet (UV) detection [5–9] set at 254 nm or 255 nm or by mass spectrometry [10–13]. The techniques using UV detection or mass spectrometry exhibit comparable lower limits of quantitation (LOQs) ranging from 0.005 mg/L to 0.2 mg/L for the former [5–9] and from 0.005 mg/L to 0.15 mg/L for the latter [10–13]. With regard to the bioassay, no formal LOQ was determined but the technique was judged acceptable down to 0.25 mg/L according to Perea et al. [7]. Nevertheless, the bioassay, which measures activity rather than a quantity, is not suitable for patients receiving co-medication and is inferior to chromatographic methods in terms of precision and accuracy [8]. In addition to plasma levels, Zhou et al. [11] have proposed a method for the determination of voriconazole in aqueous humour using mass spectrometry detection with a LOQ of 0.005 mg/L. In addition, Rengelshausen et al. [12] have validated a liquid chromatographic method with mass spectrometric detection for determination in human urine with a LOQ of 0.05 mg/L. Although voriconazole is extensively biotransformed (see below), no assay has been published reporting the quantification and separation of the unlabelled parent drug and its metabolites.

Capillary electrophoresis has been used for the determination of voriconazole in solutions and in human liver microsome extracts but no real pharmacokinetic application has been proposed [14,15]. Capillary electrophoresis is a relatively recent analytical technique that presents the advantages of low injected sample volume, high separation efficiency and low consumable expense.

5. Pharmacokinetic properties

The pharmacokinetic properties of voriconazole have been investigated in healthy male volunteers and in patients. Most studies have used liquid chromatographic methods unless otherwise specified.

5.1. Absorption

Given orally twice a day in healthy male volunteers at dosages ranging from 200 mg to 400 mg, voriconazole formulated in capsules is rapidly absorbed, with a mean time to peak plasma concentration (T_{max}) varying between 1.43 h (200 mg) and 1.81 h (400 mg) [16]. The corresponding maximum plasma concentration (C_{max}) was 1.88 mg/L (200 mg), 4.84 mg/L (300 mg) and 5.27 mg/L (400 mg) when determined after 7 days of oral dosing [16]. The C_{max} as well as the area under the plasma concentration–time curve (AUC) increased non-linearly, suggesting, in part, the saturation of a first-pass effect. However, bioavailability is high and does not seem to vary significantly with dose; it has been estimated to be ca. 90% [17]. Calculated from the data of Purkins et al. [16] (i.e. mean AUC_{oral}/mean $AUC_{i.v.}$), the bioavailabilities are 82.8% (200 mg), 100% (300 mg) and 85% (400 mg). Therefore, the rate of elimination by both routes appears to decrease with increasing dose.

Oral pharmacokinetics have been studied in 18 patients who were administered twice-daily voriconazole 200 mg or 300 mg formulated in tablets [18]. The T_{max} was achieved in 1.7–3 h but was determined with less accuracy than in healthy volunteers given the smaller number of time points (6 versus 12 over 12 h). The C_{max} increased between Day 1 and Day 14 from 0.9 mg/L to 3 mg/L (200 mg) and from 1.63 mg/L to 4.66 mg/L (300 mg), showing accumulation on iterative dosing. The absolute bioavailability of voriconazole in patients has not been published (lack of coupled i.v. data). According to the authors, the kinetic characteristics in patients are comparable with those in healthy volunteers.

Pharmacokinetics of crushed voriconazole tablets suspended in water (280 mg twice daily) and delivered by a jejunostomy tube have been investigated in a patient with *Candida glabrata* infection [19]. The C_{max} was ca. 2.5 mg/L and trough concentrations ranged between 1.4 mg/L and 1.75 mg/L when determined in serum between Day 2 and Day 28. These values appeared slightly inferior to those determined after oral administration. In addition, C_{max} values did not increase from Day 2 to Day 28, contrasting with previously published data showing accumulation. Since publication of this paper, the oral solution has been made available. If delivery of voriconazole by a jejunostomy tube appears feasible, it does not need the tablets to be crushed. Similarly, plasma concentrations of voriconazole given at 200 mg twice daily via a nasogastric tube (after crushing and suspending in water) have been determined in eight critically ill patients after a mean duration of treatment of 16 days (range, 3–44 days) [20]. The C_{max} (measured at 2 h post dosing) and trough concentrations were 6.4 mg/L (standard deviation (S.D.), 4.3) and 4.6 mg/L (S.D., 2.8), respectively.

These values appeared higher than those previously reported after oral administration of the solid form [16,19]. According to the authors, nasogastric administration can constitute an alternative to i.v. injection for mechanically ventilated patients.

5.2. Distribution

The plasma protein binding of voriconazole is moderate (ca. 58%) [17]. In line with the localisation of certain fungal infections, voriconazole diffusion has been investigated in the central nervous system (CNS) and in the eye. Brain concentrations have been measured in post-mortem specimen from two patients [21]. The concentrations were 11.8 mg/g (dosage, 7.2 mg/kg/day) and 58.5 mg/g (dosage, 4.5 mg/kg/twice a day). Voriconazole has also been determined in the cerebrospinal fluid (CSF) as a surrogate of CNS penetration. When obtained from 14 patients, the CSF concentrations ranged from 0.08 mg/L to 3.93 mg/L (median, 0.65 mg/L) at 1–10 h after administration. Plasma concentrations were determined on the same day and varied from <0.01 mg/L to 7.23 mg/L (median, 1.08 mg/L), leading to a median CSF/plasma ratio of 0.46 (range, 0.22–1) [22]. Therefore, voriconazole exhibits significant transport across the blood–brain barrier. The molecular mechanism underlying voriconazole passage remains unknown. Moreover, these concentrations are in the same range as the MIC_{90} (the minimal inhibitory concentration for 90% of the organisms) for fungal pathogens. Clinically, some case reports have described successful treatment of CNS fungal infections by voriconazole in refractory patients [21,23–27].

Fungal endophthalmitis is rare but constitutes a devastating infection given, in part, the difficulty for drugs to reach the avascular vitreous tissue. Intraocular penetration of oral voriconazole has been characterised by Hariprasad et al. [28] in 14 patients undergoing vitrectomy surgery. Following two 400 mg doses separated by 12 h, voriconazole was analysed in vitreous fluid, aqueous humour and plasma samples by liquid chromatography. The mean concentrations were 2.13 mg/L (S.D., 0.93), 0.81 mg/L (S.D., 0.31) and 1.13 mg/L (S.D., 0.57) in plasma, vitreous fluid and aqueous humour, respectively. The MIC_{90} values for common pathogens (*Aspergillus* spp., *Candida* spp.) were achieved in the eye. In this context, systemic voriconazole could lead to therapeutic concentrations in the eye, constituting an alternative to intravitreal injections (for vitreous infections) or topical application (for keratitis). However, in patients with *Fusarium* keratitis, data from case reports suggest adding topical voriconazole to systemic treatment to achieve a beneficial effect [29,30]. Given only systemically, concentrations of voriconazole in the aqueous humour might be insufficient to treat *Fusarium* keratitis [30]. Voriconazole administered intravenously (4 mg/kg twice a day) and topically lead to concentrations in the anterior chamber of the eye and in plasma of 3.2 mg/L and 2 mg/L, respectively, when measured by a bioassay [30].

Satisfactory results have been reported in 11 of 20 patients with bone aspergillosis treated by voriconazole [31]. Although kinetic data are lacking, this suggests good diffusion of voriconazole in bone tissue.

5.3. Metabolism

When assessed in six healthy volunteers, unchanged voriconazole recovered in urine and faeces accounted for only 2% of the radioactive dose, thus indicating extensive metabolism [32]. Three major metabolites whose identities have been confirmed by mass spectrometry have been found in humans [32]. The pathways involved *N*-oxidation of the fluoropyrimidine ring leading to the major circulating metabolite known as UK-121,265, hydroxylation of the fluoropyrimidine ring and methyl hydroxylation, followed for the latter two by glucuronide conjugation. The metabolite UK-121,265 represented 15% of the radioactivity in plasma and displayed a weak antifungal activity, being 100-fold less potent than the parent drug in vitro [32]. Identification of the isoenzymes of the superfamily cytochrome P450 (CYP) responsible for the formation of UK-121,265 has been conducted in vitro by means of human liver microsomes, recombinant human CYP and inhibition experiments [33]. Formation of UK-121,265 in liver microsomes was mediated by CYP3A4, CYP2C19 and to a lesser extent CYP2C9 [33] and showed biphasic kinetics with Michaelis–Menten constant (K_m) values of 8 μM (2.8 mg/L) and 835 μM (305 mg/L). The K_m represents the unbound concentration at which the rate of conversion of voriconazole to UK-121,265 is one-half the maximum.

5.4. Excretion

The total dose of voriconazole (oral or i.v. administration) is excreted in 48 h, predominantly as metabolites (98%). When determined in six healthy volunteers, the renal route accounted for 76.9% and 79.8% of an i.v. and oral radioactive dose of voriconazole, respectively. The remaining radioactivities (ca. 20%) were recovered in faeces [32]. The negligible kidney elimination of voriconazole as unchanged drug is emphasised by its very low renal clearance (ca. 1.6 mL/min) [12].

5.5. Pharmacokinetic parameters

The pharmacokinetics of oral and i.v. voriconazole in adults are presented in Tables 1 and 2, respectively. They have mostly been documented in healthy volunteers and the characteristics relative to elimination have not been determined in patients. The elimination process has sometimes been estimated using the elimination constant (k^{el}) instead of the more commonly used terminal half-life. Therefore, in

Table 1
Pharmacokinetic parameters (mean (standard deviation)) for oral voriconazole in adults (liquid chromatographic assay)

No. of patients	Dose (mg)	Sampling period (h)	C_{max} (mg/L)	T_{max} (h)	$AUC_{0-12\,h}$ (mg h/L)	V_d (L)	CL (mL/min)	$t_{1/2}$ (h)	Reference
16 (healthy volunteers)	400 (Day 1)	24	2.56 (0.56)	1.85 (0.94)	12.7 (4.16)[a]	227 (80.5)	390 (192)[b]	8.18 (4.73)	[12]
14 (healthy volunteers)	200 every 12 h (Day 7)	12	1.88	1.5	9.7	160.2	333	4.71[c]	[16]
7 (healthy volunteers)	300 every 12 h (Day 7)	12	4.83	1.43	30.94	106.9	139	6.6[c]	
14 (healthy volunteers)	400 every 12 h (Day 7)	12	5.27	1.81	37.54	123.8	135	7.21[c]	
9	200 every 12 h (Day 1)	12	0.90	2.8 (2.3)	4.04	N.R.	N.R.	N.R.	[18]
	200 every 12 h (Day 7)	12	2.99	1.7 (1)	20.3	N.R.	N.R.	N.R.	
9	300 every 12 h (Day 1)	12	1.63	1.7 (1)	7.8	N.R.	N.R.	N.R.	
	300 every 12 h (Day 7)	12	4.66	3 (1.5)	36.5	N.R.	N.R.	N.R.	

C_{max}, peak concentration; T_{max}, time to reach peak concentration; AUC, area under the serum concentration–time curve; V_d, volume of distribution; CL, clearance calculated as dose × bioavailability/mean AUC; $t_{1/2}$, terminal half-life; N.R., not reported.
[a] From 0 to 10 h.
[b] Oral systemic clearance.
[c] Calculated as 0.693/elimination constant.

Tables 1 and 2 we report the mean terminal half-lives through the equation 0.693/mean k^{el}.

Voriconazole (oral or i.v.) exhibits non-linear pharmacokinetics (i.e. dose-dependent clearance) [16]. After i.v. administration at doses ranging from 3 mg/kg to 5 mg/kg twice a day, the mean total clearance (determined at Day 7) decreased from 233 mL/min to 100 mL/min. Conversely, the mean half-life increased from 5.29 h to 8.15 h. Likewise, after oral administration at doses ranging from 200 mg to 400 mg twice a day, the total clearance (calculated at Day 7) decreased from 333 mL/min to 135 mL/min and the mean half-life increased from 4.71 h to 7.21 h. The authors suggest that the non-linear behaviour is attributable to saturable metabolism. Regrettably, concentrations of the metabolite UK-121,265 were not determined. Dose-dependent kinetic non-linearity could also be the consequence of inhibition of biotransformation by a metabolite.

The $AUC_{0-12\,h}$ values for oral voriconazole increased five-fold with repeated doses (200 mg or 300 mg twice daily) over a 14-day period (Table 1) [18]. When considering mean trough concentrations determined on Days 1, 4, 7, 10 and 14, steady state was achieved between Days 4 and 7 for patients receiving 200 mg or 300 mg twice daily. Likewise, in healthy volunteers receiving i.v. voriconazole (6 mg/kg twice daily on Day 1 followed by 6 days at 4 mg/kg twice daily), steady-state trough concentrations were reached on Day 4 [16]. As for dose-dependent clearance, saturation of elimination has been suggested, although the accumulation could also be due to a metabolite that inhibits transformation of the parent drug.

6. Special patient populations

6.1. Children

Voriconazole is approved in children aged >2 years. Pharmacokinetics of voriconazole given intravenously (3 mg/kg or 4 mg/kg, single or multiple doses) have been investigated in 35 immunocompromised children (aged 2–11 years) [34]. Only the values of C_{max} were reported (Table 3). The parameters relative to elimination were not determined, perhaps owing to the small number of time points ($n = 4$). Consequently, pooled data obtained from the 35 children have been integrated in a population pharmacokinetic analysis. The simulation suggests linear pharmacokinetics (between 3 mg/kg and 4 mg/kg) with a half-life of 7.5 h and a clearance of 6.7 mL/min/kg, thus contrasting with the adult data (dose-dependent clearance). In addition, at a therapeutic dose of 4 mg/kg, clearance of i.v. voriconazole appears lower in healthy adults than in children (2 mg/min/kg versus 6.7 mg/min/kg). Nevertheless, according to the official labelling, the dosage of i.v. voriconazole per kg is identical in the adult and paediatric patient. With regard to the oral route, the pharmacokinetics of voriconazole in children have not been reported.

Table 2
Pharmacokinetic parameters (mean) for intravenous voriconazole (liquid chromatographic assay, sampling period 12 h) in adults

No. of patients	Dose (mg/kg), 1 h infusion	C_{max} (mg/L)	$AUC_{0–12\,h}$ (mg h/L)	V_d (L) calculated for 70 kg	CL (mL/min) calculated for 70 kg	$t_{1/2}$ (h)	Reference
14 (healthy volunteers)	3 every 12 h (Day 7)	3	13.91	131	233	5.29	[16]
7 (healthy volunteers)	4 every 12 h (Day 7)	5.4	29.46	97.3	140	7.87	
14 (healthy volunteers)	5 every 12 h (Day 7)	7.18	43.37	63.2	100	8.15	

C_{max}, peak concentration; AUC, area under the serum concentration–time curve; V_d, volume of distribution; CL, clearance; $t_{1/2}$, terminal half-life calculated as 0.693/elimination constant.

Table 3
Pharmacokinetic parameters (mean) for intravenous voriconazole (liquid chromatographic assay, sampling period 12 h) in children

No. of children	Dose (mg/kg), 1 h infusion	C_{max} (mg/L)	$AUC_{0–12\,h}$ (mg h/L)	CL (mL/min/kg)	$t_{1/2}$ (h)	Reference
6	3 (Day 1)	2.2 (range, 1.77–2.48)	N.R.	N.R.	N.R.	[34]
5	4 (Day 1)	2.52 (range, 1.65–3.56)	N.R.	N.R.	N.R.	
22	3 (Day 4)	2.61	N.R.	N.R.	N.R.	
20	4 (Day 8)	2.37	N.R.	N.R.	N.R.	

C_{max}, peak concentration; AUC, area under the serum concentration–time curve; CL, clearance; $t_{1/2}$, terminal half-life.
N.R., not reported.

6.2. Renal dysfunction

Voriconazole is predominantly cleared by biotransformation leading to metabolites with unknown or only weak pharmacological activity and with ca. 78% being excreted by the kidneys. According to the manufacturer, renal insufficiency has no impact on voriconazole pharmacokinetics and does not require a reduction in the dosage when given orally. The i.v. composition of voriconazole is formulated with a cyclodextrin (sulfobutylether β-cyclodextrin) to improve its solubility. Cyclodextrin has been shown to accumulate in patients with moderate renal dysfunction (creatinine clearance <50 mL/min) receiving i.v. voriconazole. The manufacturer recommends using the oral form preferentially, although cyclodextrins are regarded as essentially non-toxic and non-irritant.

In addition, data from five patients with end-stage renal disease on peritoneal dialysis indicate that the passage of voriconazole in the peritoneal dialysate is minimal (less that 1% of the dose in 24 h). No dose adjustment is needed for these patients [35].

6.3. Hepatic dysfunction

Few kinetic data are available in the patient with hepatic impairment. Considering the extensive metabolism of voriconazole, it is recommended to reduce the dosage in patients with chronic liver disease. Patients with cirrhosis (Child–Pugh classes A and B) should receive half the maintenance dose preceded by a standard loading dose, based on previously published results [36]. Six patients with moderate cirrhosis (Child–Pugh class B) were shown to exhibit one-half the oral clearance of voriconazole and exposure to UK-121,265 compared with six patients with normal hepatic function [36]. Patients with severe chronic cirrhosis (Child–Pugh class C) have not been studied. Dose adjustment is not recommended in patients with acute dysfunction as assessed by elevation of enzymes (alanine aminotransferase, aspartate aminotransferase).

7. Factors influencing pharmacokinetics

7.1. Age

The pharmacokinetics of voriconazole in the elderly have not been reported. According to the official labelling, no dose adjustment is needed.

7.2. Body weight

In children, body weight has been shown to account for the kinetic intervariability of i.v. voriconazole based on a population pharmacokinetic study [34]. This modelisation partly supports the use of body weight in the paediatric regimen although the clinical impact of kinetic variability is unknown.

In adult patients, the i.v. dosage is also based on body weight. This supposes that body weight is a significant determinant of voriconazole clinical activity. In fact, according to Trifilio et al. [37], the relationship between serum levels and dose adjusted to body weight is weak. Furthermore, the impact of kinetic variability on voriconazole activity (pharmacodynamics) remains unknown, although data from three case reports [38] indicate that toxic events (hallucinations, hypoglycaemia and electrolyte disturbance) could be linked to high plasma levels (trough concentrations, 9–17 mg/L). Nevertheless, to our knowledge no formal relationships have been established on the one hand between body weight and kinetics and on the other hand between kinetics and clinical

parameters. The absence of significant relationships could lead to a fixed dose in adult patients, as for fluconazole or itraconazole.

7.3. Pharmacogenetics

Pharmacogenetics deals with, among other things, the impact of genetic variants encoding kinetic determinants (enzymes, transporters) on the pharmacokinetics of drugs. As seen before, biotransformation of voriconazole into its main metabolite (UK-121,265) involves CYP3A4, CYP2C19 and CYP2C9. Coding mutations for the *CYP3A4* gene have been reported and can affect enzymatic activity. Nevertheless, these variants are rare and are considered to have a limited impact on the clearance of CYP3A4 substrates [39]. With regard to CYP2C19, some genetic variants are associated with the loss of enzymatic activity. Individuals who are carriers of two variant alleles exhibit a lower clearance of CYP2C19-metabolised drugs such as omeprazole or lansoprazole [40]. The frequency of these subjects, also called poor metabolisers, is ca. 2% in the Caucasian population and can reach 14% among Asian individuals [40]. Thus, patients with genotypes conferring the loss of CYP2C19 enzymatic activity are potentially subject to an increased exposure to voriconazole. The impact of *CYP2C19* genotyping on voriconazole kinetics has been investigated in 12 healthy Japanese volunteers [41]. The triazole was given orally twice a day for 10 days at 200 mg ($n = 6$) or 300 mg ($n = 6$). Each group of six subjects included one subject with poor enzymatic activity. The two poor metabolisers exhibited exposure to oral voriconazole (AUC determined at Day 10) 5.8 and 3.8 times higher than those determined in the six patients with the wild-type gene (called extensive metabolisers) after administration of 200 mg and 300 mg, respectively. Likewise, in a German study, exposure to oral voriconazole at steady state was 2.6 times higher in two volunteers with a genotype associated with defective CYP2C19 activity than in those with the wild-type gene ($n = 8$) [12]. In contrast to omeprazole or lansoprazole, the impact of *CYP2C19* genotype on the clinical effects of voriconazole has not yet been determined. Establishment of a dosage regimen based on the identification of *CYP2C19* genetic variants appears premature even if a test is now commercially available. Currently, genotyping for pharmacokinetic purposes is performed in a few centres and mostly concerns the thiopurines (mercaptopurine, thioguanine).

7.4. Food

The effect of food on voriconazole distribution has been studied in 12 healthy volunteers [42]. At steady state (Day 7), the $AUC_{0–12\,h}$ of oral voriconazole (200 mg twice daily) given with a high-fat breakfast was decreased by 22% compared with that obtained 2 h before a low-fat breakfast. The package insert recommends intake of voriconazole 1 h before or 2 h after a meal.

8. Drug–drug interactions

Pharmacokinetic interactions commonly occur via drug-metabolising enzymes or drug transporters. As mentioned earlier, voriconazole is extensively biotransformed, mostly by CYP3A4 and CYP2C19, into the main metabolite. Inhibitors of CYP3A4 and CYP2C19 or inducers (i.e. drugs activating orphan nuclear receptors) would be expected to influence voriconazole kinetics. On the other hand, and considering its congeners (miconazole, fluconazole, ketoconazole and itraconazole) [43], the potential for voriconazole to modify the kinetics of co-administered drugs appears high. However, from a molecular perspective, information regarding these processes is scarce. Whether voriconazole interferes with drug uptake or efflux transporters, orphan nuclear receptors or inhibits enzymatic activities or drug transport remains poorly reported. Most of the studies exploring drug–drug interactions have been performed in healthy volunteers and have been conducted by the manufacturer.

8.1. Drugs that change voriconazole pharmacokinetics

8.1.1. Drugs that potentially increase voriconazole concentrations

8.1.1.1. Erythromycin. Erythromycin is a macrolide antibacterial known to inhibit CYP3A4 activity and to increase the concentrations of several co-administered drugs. More precisely, erythromycin is a mechanism-based inhibitor of CYP3A4 [44]. The macrolide forms a reactive metabolite via CYP3A4 that binds covalently and inactivates the enzyme. Compared with reversible inhibitors such indinavir (see below), it is assumed that irreversible inhibitors are more frequently involved in drug–drug interactions because the inactivated CYP3A4 must be replaced by newly synthesised enzyme [44]. The influence of oral erythromycin (1 g twice daily) on voriconazole pharmacokinetics has been studied at steady state in 20 healthy volunteers who were given the azole orally (200 mg twice daily) [45]. Compared with placebo, erythromycin did not significantly affect voriconazole $AUC_{0–12\,h}$ (9.45 mg h/L versus 8.65 mg h/L). Unfortunately, plasma concentrations of the main metabolite (i.e. UK-121,265 known to be produced via CYP3A4) were not determined. Overall, these finding suggest that irreversible CYP3A4 inhibitors such as erythromycin do not alter voriconazole activity.

8.1.1.2. Indinavir. The antiretroviral drug indinavir is a potent reversible CYP3A4 inhibitor in vitro [46] and has been involved in significant increases in exposure to co-administered drugs in vivo [47]. The combination of indinavir (800 mg thrice) with oral voriconazole (200 mg twice) in 31 healthy volunteers did not lead to significant kinetic alterations of either drug at steady state [48]. No adjustment of dosage is required when indinavir and voriconazole are combined. Overall, the absence of effects of CYP3A4 inhibitors in vivo contrasts with data obtained in vitro. Hence,

ketoconazole, a reversible CYP3A4 inhibitor at low dose (2.5 μM), has been shown to decrease by 60% the metabolism of voriconazole (at 25 μM or 8.72 mg/L) in human liver microsomes [33].

8.1.1.3. Ranitidine and cimetidine. Ranitidine and cimetidine are histamine H2 receptor antagonists used in gastrointestinal disorders. In vitro, cimetidine has been shown to inhibit several CYP isoenzymes (CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 and CYP1A2) [49]. Ranitidine is considered to be a weak CYP inhibitor compared with cimetidine. Co-administration of oral cimetidine (400 mg twice daily) with oral voriconazole (200 mg twice daily) to 12 healthy volunteers lead to a 23% increase in the azole $AUC_{0–12\,h}$ at steady state [50]. This increase was judged to be clinically irrelevant (in terms of safety). As expected, oral ranitidine (150 mg twice daily) has no impact on voriconazole plasma concentrations [50].

8.1.1.4. Omeprazole. The proton pump inhibitor omeprazole is a substituted benzoimidazole that has been shown to inhibit CYP2C19, CYP2C9 and CYP3A4 in vitro [51]. Nevertheless, metabolic drug interactions of clinical significance appear uncommon with omeprazole. When combined orally with voriconazole (200 mg twice daily), omeprazole (40 mg daily) increased the exposure of the antifungal agent by 40% at steady state (Day 10) in 18 healthy volunteers [52]. This interaction is not considered clinically significant and thus no dose reduction is recommended.

8.1.2. Drugs that potentially decrease voriconazole concentrations

Agents that decrease exposure of co-administered drugs, such as rifampicin, are often called enzymatic inducers [53], although they can also enhance the expression of drug transporters (i.e. P-glycoprotein (P-gp) or ABCB1) [54]. Inducers do not directly interact with enzymes or transporters. In fact, they activate proteins called orphan nuclear receptors, such as pregnane X receptor (PXR or SXR) or constitutive androstane receptor (CAR) [55–57]. These nuclear receptors or xenosensors act as transcriptional factors regulating the expression of genes coding for CYP and transporters. Agents that activate nuclear receptors act as pleiotropic inducers increasing the expression of CYP isoenzymes or transporters and hence the elimination of associated drugs.

8.1.2.1. Rifampicin and rifabutin. The antibacterial agents rifampicin, and probably rifabutin, activate PXR and CAR [58–61]. They are involved in numerous metabolic and non-metabolic pharmacokinetic interactions mostly attributable to increases in CYP3A4, CYP3A5 or CYP2C9 enzymatic activity or to P-gp expression [62]. Although both compounds show comparable in vitro induction potencies, rifampicin is a more potent inducer than rifabutin in humans, presumably attributable to its slower elimination [63]. It must be stressed that besides induction, rifampicin also possesses inhibitory properties. Indeed, the antibacterial has been show to increase transiently exposure of agents such as the antifungal caspofungin [64]. This effect could be attributable to the inhibition of caspofungin hepatic uptake via the transporter OATP 1B1 (OATP-C or SLC21A6) [65].

Previously published data reported major reductions in voriconazole exposure at steady state when combined with rifampicin (600 mg once a day for 2 weeks) or rifabutin (300 mg once a day for 2 weeks) in healthy males [66]. AUCs for oral voriconazole decreased by 95.5% and 78.2% in the presence of rifampicin and rifabutin, respectively. According to the package insert, association of voriconazole with rifampicin is contraindicated. Combination with rifabutin must be avoided.

8.1.2.2. Phenytoin. Phenytoin is an inducer of human CYP3A4 and CYP2B6, presumably via activation of the nuclear receptors PXR and CAR, respectively [67,68]. Not surprisingly, voriconazole $AUC_{0–12\,h}$ decreased at steady state by 70% when combined with phenytoin (300 mg once daily for 2 weeks) in 10 healthy volunteers [69]. Again, this association should be avoided.

8.1.2.3. St John's wort. The herbal remedy St John's wort is an extract made from the plant *Hypericum perforatum* that is proposed as an over-the-counter antidepressant. The use of St John's wort with co-medications has lead to clinically relevant interactions resulting from a decrease in exposure to the associated drug [70]. St John's wort has been shown to induce CYP3A4, CYP2C9, CYP2C19, CYP2C8 and P-gp [70]. Regarding CYP3A4 and CYP2C9, the molecular mechanism of induction is partly attributable to the interaction of hyperforin (a constituent of St John's wort) with PXR [60,71].

Co-administration of St John's wort (300 mg three times daily for 2 weeks) lead to a 59% reduction in exposure to voriconazole when given orally (single dose of 400 mg) to 16 healthy men [12]. The terminal half-life decreased from 8.18 h (S.D., 4.73) to 4.95 h (S.D., 4.95). Interestingly, the two volunteers with defective CYP2C19 activity exhibited a decrease in voriconazole $AUC_{0–infinity}$ (39% and 56%), suggesting that the interaction was mainly attributable to CYP3A4 induction [12]. In addition to these effects observed on repeated dosing, St John's wort is also known to possess inhibitory properties (similar to rifampicin) when given as a single dose, causing increases in concentrations of co-administered drugs. Therefore, voriconazole C_{max} was shown to increase by 22% at steady state after a single dose of St John's wort, associated with a decrease in the terminal half-life (from 8.18 h to 6.37 h) [12]. Oral clearance remained unchanged. This transient alteration is unlikely to be clinically relevant. The mechanism is unclear and could be attributable to a change in absorption (although voriconazole bioavailability is ca. 90%) or distribution. Globally, St John's wort

must be stopped when treatment with voriconazole is initiated.

8.2. Drugs whose kinetics are altered by voriconazole

As seen before, studies exploring the potential for voriconazole to induce or inhibit the activities of enzymes or transporters such as CYP3A4, CYP2C9, CYP2C19 and P-gp have not yet been published. Voriconazole (as well as fluconazole and itraconazole) at 10 μM (3.49 mg/L) did not to inhibit CYP1A2, CYP2D6 and CYP2E1 activities in human liver microsomes [72]. This could suggest that metabolic interactions with drugs whose biotransformation is significantly mediated by these CYP enzymes are unlikely. Nevertheless, voriconazole increases plasma concentrations of several drugs although the molecular mechanisms underlying these modulations are not reported.

8.2.1. Tacrolimus

Tacrolimus is an immunosuppressive agent whose kinetic variability is linked to toxic effects and particularly nephrotoxicity [73]. Thus, the official labelling (in France) recommends adapting the dosage of oral tacrolimus based on the determination of trough blood concentrations. Tacrolimus oral pharmacokinetics are characterised by a low and variable bioavailability (25%) and metabolic elimination [74]. From a molecular viewpoint, CYP3A4 (liver and enterocytes) and P-gp (enterocytes) are considered to be the major kinetic determinants [74]. Co-administration of voriconazole (200 mg twice a day) and tacrolimus (2 mg) in a liver transplant patient led to a 10-fold increase in the trough concentration of the immunosuppressive agent (from 2.3 μg/L to 23.4 μg/L), suggesting inhibition of hepatic biotransformation and a potential limitation of an intestinal first-pass effect [75]. The lack of complete kinetic data impedes the identification of the site of interaction. In vitro, the concentration of voriconazole necessary to inhibit the metabolism of tacrolimus (IC_{50}) in human liver microsomes was 10.4 mg/L (ca. five-fold the mean C_{max} in healthy volunteers receiving 200 mg orally) and did not predict the amplitude of the increase [75]. The molecular mechanism of the interaction remains unknown. Co-administration of voriconazole should strengthen the monitoring of tacrolimus blood concentrations.

8.2.2. Sirolimus

Sirolimus is an oral immunosuppressive agent considered to be poorly absorbed (estimated bioavailability, 15%) and that is eliminated by the biliary route partly as metabolites [76]. Unpublished data from the manufacturer suggest that sirolimus is metabolised via CYP3A4 and is transported by P-gp. Three patients receiving sirolimus (0.75–4 mg daily) associated with voriconazole (200 mg twice daily) showed a 5.2- to 12.9-fold increase in the immunosuppressant dose-normalised trough blood concentrations (i.e. from 3–7.4 μg/L to 12.8–29 μg/L) [77]. The combination of these two drugs is contraindicated in France.

8.2.3. Cyclosporin

The immunosuppressant cyclosporin is eliminated by biotransformation via CYP3A4 [78]. The oral bioavailability is low and variable, attributable to an intestinal first-pass effect involving P-gp [79]. Two papers reported modifications of cyclosporin blood concentrations by voriconazole [80,81]. First, administration of voriconazole (200 mg twice daily by mouth) to seven renal transplant subjects receiving stabilised oral cyclosporin therapy (150–375 mg/day) lead to a 1.7-fold increase in the immunosuppressant $AUC_{0-12\,h}$. It should be stressed that C_{max} and T_{max} were not affected by voriconazole, suggesting that the azole has little effect on the first-pass effect of cyclosporin [80]. Second, a case report [81] mentioned the drop in cyclosporin trough blood concentrations after discontinuation of voriconazole in a 14-year-old patient, from 0.154–0.184 mg/L to 0.056–0.111 mg/L. Overall, cyclosporin blood concentrations must be carefully monitored when associated with voriconazole.

8.2.4. Digoxin

Digoxin is eliminated by renal and biliary excretion and by intestinal secretion. Metabolism of the cardiac glycoside is negligible. Theoretically, only non-metabolic interactions can be anticipated with digoxin. The apical drug transporter P-gp mediates the process of elimination and the limitation of absorption after oral administration [82]. Moreover, it is assumed that drug–drug interactions with quinidine [83] or ritonavir [84] resulting in elevated concentrations of the glycoside are attributable to the inhibition of P-gp transport. Voriconazole (200 mg twice daily) did not alter the pharmacokinetics of oral digoxin at steady state (0.25 mg daily) in 12 healthy volunteers [85]. This suggests that voriconazole does not interfere with P-gp-mediated drug transport in vivo. According to the manufacturer (unpublished data), voriconazole is neither a substrate nor an inhibitor of P-gp.

8.2.5. Warfarin

A pharmacodynamic interaction has been explored between voriconazole (300 mg twice a day orally) and the anticoagulant warfarin (30 mg single dose) by measuring the prothrombin time in 17 healthy volunteers [86]. The kinetics of warfarin were not determined. The mean maximal change in the prothrombin time (observed between 36 h and 48 h post dosing) significantly increased from 8 s (placebo) to 17 s (voriconazole). This interaction is likely due to a kinetic mechanism involving inhibition of the biotransformation of warfarin (warfarin is eliminated by metabolism). As recommended by the official labelling, prothrombin time should be carefully monitored in patients receiving the two drugs.

8.2.6. Phenytoin

Phenytoin is an anticonvulsant drug with a narrow range of therapeutic serum concentrations. It is eliminated by biotransformation probably mediated by CYP2C9 and CYP2C19 [87]. Data from 15 healthy volunteers indicated that oral voriconazole (400 mg twice a day) increased by

85% the exposure to phenytoin (300 mg once a day), from 197 mg h/L to 364 mg h/L [69]. As seen before, voriconazole dosage must be increased to compensate for the induction of elimination by phenytoin. Unfortunately, it is associated with elevated and potentially toxic levels of the anticonvulsant. Given the mutual nature of the interaction, this combination should be avoided.

8.2.7. Mycophenolic acid

Mycophenolic acid is an immunosuppressant metabolite resulting from de-esterification of the prodrug mycophenolate mofetil. Mycophenolic acid is also available as a sodium salt formulated in gastroresistant tablets. Mycophenolic acid is eliminated by glucuronidation followed by renal excretion [88]. A study performed in 24 healthy volunteers has indicated that voriconazole (200 mg twice a day orally) did not alter the kinetics of mycophenolic acid and its glucuronide metabolite after ingestion of a single dose of the prodrug (1 g) [89].

9. Conclusions

Voriconazole is characterised by non-linear metabolic elimination and a high bioavailability when given orally. In addition, drug exposure increases with repeated administration. Antifungal treatment failures are anticipated when voriconazole is combined with a drug interfering with orphan nuclear receptors ('inducers'). In addition, voriconazole has a great potential to alter the pharmacokinetics of co-administered drugs. Several significant interactions have been reported, but numerous others are suspected or remain unpublished leading in some cases to contraindications, as mentioned in the official labelling. Thus, compared with other azole antifungal agents, it appears premature to compare the frequencies of drug–drug interactions. Moreover, considering the advent of antifungal combinations, it will be interesting to explore kinetic interactions between voriconazole and echinocandins (i.e. caspofungin). Therefore, the publication of data reporting the interaction of voriconazole with kinetic determinants is awaited. A better understanding of these molecular processes could contribute to a more effective prediction of interactions.

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