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REVIEW ARTICLE

Pharmacokinetic profile of the antifungal agent posaconazole

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ABSTRACT

Posaconazole is a recent triazole antifungal agent currently available in an oral suspension. It is approved in the treatment of various refractory invasive fungal diseases and for prophylaxis in high-risk patients. This review presents the published clinical pharmacokinetic data of posaconazole. Aspects regarding absorption, distribution, elimination, and pharmacokinetic interactions are also discussed.

Key words
Drug-drug interactions; Pharmacokinetics; Posaconazole

RÉSUMÉ

Le posaconazole est un agent antifongique récent, appartenant à la classe des triazolés et disponible sous forme de suspension buvable. Il est indiqué dans le traitement d'infections fongiques invasives réfractaires ainsi qu'en prophylaxie chez des patients à haut risque. Cette mise au point présente les données pharmacocinétiques publiées du posaconazole chez l'homme. Les aspects concernant l'absorption, la distribution, l'élimination, et les interactions médicamenteuses sont notamment abordées.

Mots clés
Interactions médicamenteuses; Pharmacocinétique; Posaconazole;

RESUMEN

Posaconazole es un antimicótico triazol relativamente nuevo, disponible en forma de suspensión oral. El fármaco está aprobado para el tratamiento de de diversas micosis refractarias e invasivas así como para la profilaxis en pacientes de alto riesgo. Esta revisión presenta los datos farmacocinéticos del posaconazol. También se discuten aspectos relacionados a la absorción, distribución, eliminación e interacciones medicamentosas.

Palabras clave
Interacción medicamentosa; Farmacocinética; Posaconazol

INTRODUCTION

Posaconazole (formerly SCH56592) is a recent systemic antifungal agent (approved in Europe and in the United States in 2006) that belongs to the azoles chemical family. Currently, the pharmacological treatment of invasive fungal diseases comprises of the polyenes (amphotericin B and its lipidic/liposomal formulations), the azoles, the echinocandins (caspofungin, micafungin, anidulafungin), the alkylamines/thiocarbamates (terbinafine), and the fluoropyrimidines (fluorocytosine).

Other than ketoconazole, all commonly used systemic azoles are triazoles (three nitrogen in the 5-membered azole ring). This group currently in-

cludes fluconazole, itraconazole, voriconazole and posaconazole. In the European Union, posaconazole is licensed for the treatment of adult patients with various refractory invasive infections (aspergillosis, fusariosis, chromoblastomycosis, and coccidioidomycosis) and those with oropharyngeal candidiasis. It is also approved as prophylactic treatment of invasive fungal infections in high-risk patients such as those receiving chemotherapy for acute myelogenous leukemia or those treated for a severe graft-versus-host disease after allogeneic hematopoietic stem-cell transplantation. This review summarizes the published pharmacokinetic data for posaconazole in humans.

PHARMACOLOGICAL PROPERTIES

Posaconazole is an enzyme inhibitor that blocks the synthesis of ergosterol, a constituent of fungal membranes, and thereby hinders the growth of the microorganism. Posaconazole binds in the active site of the P-450-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 the function of the fungal membrane [3]. The IC_{50} (concentration leading to a 50% decrease in ergosterol synthesis in fungi extracts) are lower than the MIC (minimal inhibitory concentrations) for some Candida species, around 7 µg L^{-1} for *Candida albicans* (MIC: 60 µg L^{-1}) and 300 µg L^{-1} for *Candida glabrata* (MIC: 4 mg L^{-1}) [3]. Regarding *Aspergillus strains*, posaconazole displays IC_{50} comparable to MIC, approximately 30 µg L^{-1} [3]. Posaconazole is a broad-spectrum antifungal showing *in vitro* and *in vivo* activity against *Candida spp*., including most fluconazole-resistant *C albicans* and *C krusei*, *Aspergillus spp*., including some itraconazole, voriconazole and amphotericin B-resistant *Aspergillus fumigatus*, *Cryptococcus neoformans*, Fusarium species, zygomycetes and endemic fungi such as *Blastomyces dermatitidis*, *Coccidioides immitis* [4].

Drug formulation and administration

Posaconazole is administered orally and, currently, is only formulated in a suspension in polysorbate 80 (surfactant) at 40 mg mL^{-1}. A tablet form has been investigated but has not been licensed due to dissolution problems. Hence, exposure to posaconazole after intake of the suspension was enhanced by 1.3 fold when compared with the tablet [5]. In addition, an intravenous formulation is in development. Posaconazole is administered at 400 mg once every 12 hours or 200 mg once every 6 h in the management of refractory invasive infections. The oral regimen for oropharyngeal candidiasis is 200 mg the first day and then 100 mg once a day for 13 days. For prophylaxis, it is given at 200 mg three times daily. To insure maximal absorption (see below), posaconazole must be taken with a meal or a nutritional supplement.

Analytical methodology

Structurally, posaconazole (molecular weight or MW: 700.8) is highly related to itraconazole (MW: 705.6) mostly differing by the replacement of 2 fluorine atoms by two chlorine in the phenyl ring. As with itraconazole, posaconazole is very lipophilic and is insoluble in water at physiologic pH. To date, various validated assays regarding the analysis of posaconazole in human plasma and urine have been published [6] [7] [8] [9] [10]. As an antiinfective agent, voriconazole has been quantitated in plasma by a classical microbiological assay (bioassay) [6], by liquid chromatography with ultraviolet (UV) detection set at 255 or 262 nm [7] [8] or tandem mass spectrometric detection [9] [10].

The techniques using UV detection or mass spectrometry exhibit comparable lower limits of quantitation (LOQ) in plasma (range 0.001 mg L^{-1} to 0.050 mg L^{-1}) that are sufficient for determination of terminal half-lives at therapeutic dosages. The LOQ in urine was 0.035 mg L^{-1} [10]. The LOQ in plasma (bioassay) was 0.62 mg L^{-1} [6]. The bioassay, which measures an activity rather than a quantity, is not suitable for patients receiving an association and is inferior to chromatographic methods in terms of precision and accuracy. However, it constitutes a means to detect the presence of eventual active metabolites.

Absorption

Posaconazole is a high permeability/low solubility drug and belongs to the class II of the Biopharmaceutics Classification System (BCS) [11]. Thus, it is considered to have a high intestinal absorption after oral dosing. However, efflux transporters might affect the extent of intestinal absorption. Molecular determinants controlling intestinal absorption have partially been identified. According to the manufacturer, posaconazole interacts with the drug transporter P-glycoprotein (P-gp; also referred as ABCB1), encoded by the gene MDR1, as a 'substrate' and as an inhibitor (unpublished data). This suggests that P-gp expressed at the apical side of enterocytes might limit the transcellular passage of the azole, due to an efflux in the intestinal lumen. Unfortunately, the absolute bioavailability of oral posaconazole is unknown due to the lack of coupled intravenous kinetic data.

Table 1 Pharmacokinetic parameters for single oral dose posaconazole in adults

Subjects	Dose (mg)	Sam-pling period (h)	C_{max} (mg L^{-1})	T_{max} (h)	AUC_{0-t} (mg h^{-1} L^{-1})	Vd/F (L)	Cl/F (mL min^{-1})	$t_{½}$ (h)
Healthy volunteers*	Tablet							
6	50	120	0.11 (46)	6.3 (51)	2.3 (50)	511 (32)	389 (40)	15.9 (18)
6	100	120	0.23 (26)	7.3 (36)	6.1 (28)	431 (20)	275 (21)	18.3 (13)
6	200	120	0.33 (21)	5.8 (35)	10.3 (30)	674 (18)	341 (40)	24.5 (22)
6	400	120	0.61 (31)	6.3 (44)	19.4 (33)	781 (49)	363 (35)	24.1 (24)
6	800	120	1.3 (26)	6.2 (46)	46.9 (40)	594 (19)	320 (48)	24.4 (33)
6	1200	120	0.93 (28)	8.8 (85)	41.7 (42)	1,341 (58)	585 (73)	28.5 (26)
Patients**	Suspension							
7	200, once a day	24	0.12 ± 74	7.6	1.9 ± 1.1	NR	NR	NR
15	400, once a day	24	0.19 ± 126.7	8.2	2.9 ± 2	NR	NR	NR
7	200, qid	24	0.12 ± 58.5	4.3	2.9 ± 1.1	NR	NR	NR

C_{max} : Peak concentration; T_{max}: time to C_{max}; AUC: area under the serum concentration-time curve; Vd/F: apparent volume of distribution; Cl/F : apparent clearance, $t_{½}$: terminal half-life; NR: not reported; qid = four times a day.
Results are expressed as mean (CV %) or mean ± SD.
* Reference [12]; **Reference [13].

Table 2 Pharmacokinetic parameters for multiple oral doses posaconazole in adults

Subjects	Dose (mg)	Sampling Period (h)	C_{max} (mg L^{-1})	T_{max} (h)	AUC_{0-t} (mg h^{-1} L^{-1})	Vd/F (L)	Cl/F (mL min^{-1})	$t_{½}$ (h)
Healthy volunteers*	Tablet; twice a day (day 14)							
9	50	120	0.37 (30)	9 (34)	3.8 (36)	365 (29)	225 (34)	19.2 (16)
9	100	120	1.0 (42)	11 (16)	10.2 (40)	343 (24)	172 (32)	24.1 (20)
9	200	120	1.3 (27)	10 (19)	14.3 (27)	467 (32)	232 (34)	23.9 (26)
9	400	120	3.2 (19)	9 (32)	33.9 (21)	486 (34)	192 (25)	31 (46)
Patients**	Suspension; once daily (last day of dosing)							
7	200	24	0.26 ± 0.20	3.9	4.5 ± 2.9	NR	990.8 ± 516.7	NR
15	400	24	0.35 ± 0.16	6.9	6.4 ± 3.2	NR	1,506.7 ± 1,201.7	NR
7	200	24	0.48 ± 0.19	10.3	8.7 ±3.3	NR	1,485.5 ± 873.5	NR

C_{max} : Peak concentration; T_{max}: time to C_{max}; AUC: area under the serum concentration-time curve; Vd/F: apparent volume of distribution; Cl/F : apparent clearance, $t_{½}$: terminal half-life; NR: not reported. Results are expressed as mean (CV %) or mean ± SD. *Reference [12]; **Reference [13].

When given orally, once a day in healthy male volunteers, at single dosages ranging from 50 mg to 1,200 mg, posaconazole (in tablet form) is slowly absorbed with a mean time to peak plasma concentration (T_{max}) varying between 6 and 9 h [12].

The corresponding maximum plasma concentrations (C_{max}) increased linearly from 0.11 mg L^{-1} (50 mg) to 1.32 mg L^{-1} (800 mg) (Table 1). Above 800 mg, the exposition showed saturation (i.e., no increase in the C_{max} and in the area under the plasma concentrations-time curve or AUC) most likely attributed to its low solubility in the digestive tract fluids [12]. Oral pharmacokinetics have been studied in 29 patients who were administered once daily posaconazole 200 or 400 mg formulated in oral suspension (single dose) [13]. When compared with healthy volunteers receiving tablets, the T_{max} were comparable (7-8 h) except in patients who received the drug four times a day due to the short dosing interval (Table 1).

Distribution

The plasma protein binding of posaconazole is high, around 98% [14]. No data regarding its diffusion in specific tissues have been yet reported. For example, posaconazole has shown clinical activity in the management of central nervous system fungal infections, but its diffusion in the cerebrospinal fluid as a surrogate of CNS penetration remains to be determined [15].

Metabolism

When assessed in 8 healthy volunteers, unchanged posaconazole recovered in urine and feces accounted for 76.3% of the radioactive oral dose thus indicating a low metabolism [10].

In plasma, a glucuronide of posaconazole was the major metabolite accounting for 17.7% to 27.6% of the radioactivity [10]. *In vitro*, incubation of posaconazole in human liver microsomes resulted in the formation of a glucuronide [16]. The biotransformation was catalyzed by the uridine diphosphate-glucuronosyltransferase (UGT) 1A4. According to the microbiological assay, there is no biologically active metabolite of posaconazole in human plasma [6].

Excretion

Posaconazole appeared excreted predominantly by the biliary route as unchanged drug. When determined in 8 healthy volunteers, the feces (that also includes the unknown non-absorbed fraction) contained 76% of an oral radioactive dose of posaconazole [10]. Most of the fecal radioactivity (66.3%) was associated to the parent drug, the remainder corresponding to various minor metabolites. The renal route accounted for 14% of the oral radioactive dose of posaconazole, predominantly (10%) as unchanged drug [10].

Pharmacokinetic parameters

The pharmacokinetics of posaconazole in adults is presented in Table 1 and Table 2. Since the absolute bioavailability is unknown, the systemic clearance cannot be determined. Posaconazole exhibited linear pharmacokinetics up to 800 mg [12].

Given as a single oral dose (tablet), the mean apparent clearance ranged between 275 and 389 mL min^{-1} and the mean half-life ranged from 15.9 to 28.5 h. The apparent volume of distribution varied between 431 and 781 L. At steady state (achieved by day 10), and given twice a day (tablet), the apparent clearance was lower due to accumulation, ranging between 172 and 232 mL min^{-1}.

When compared with the single dose, the terminal half-lives (19.2 to 24.1 h) and the apparent volumes of distribution (365 to 486 L) were comparable at steady state [12]. Between Day 1 and Days 8-14, exposures (AUC_{0-24h}) increased 2-3 folds in patients who received the oral suspension [13]. This is not surprising since the dosing interval (12 h) was shorter than the terminal half-life.

SPECIAL POPULATIONS

Children

Posaconazole is currently not approved in children in the European Union. In the United States, it is approved in children 13 years of age and older for prophylaxis of Candida and Aspergillus infections. Partial pharmacokinetic data have been obtained in 12 young patients aged 8-17 years who received posaconazole oral suspension (800 mg daily in divided doses) [17]. At steady state, the plasma concentrations were judged comparable to those obtained in adults (around 0.8 mg L^{-1}). Elimination PK parameters were not reported.

Renal dysfunction

The renal route is a minor pathway for the elimination of posaconazole. Thus, its disposition is not expected to be altered by renal dysfunction. This was confirmed in a study that assessed posaconazole kinetics in 18 subjects with various degrees of renal insufficiency (creatinine clearance or Cl_{cr} ranging from < 20 mL min^{-1} to 80 mL min^{-1}) and who received a single dose (400 mg) of oral suspension [14]. Expositions (AUC extrapolated to infinity) were comparable to those calculated in healthy subjects with normal renal function (i.e. Cl_{cr} > 80 mL min^{-1}). In addition, it was shown that hemodialysis did not affect posaconazole plasma concentrations in 6 patients with severe renal insufficiency [14].

Hepatic dysfunction

Considering the biliary excretion of posaconazole, an increase in the exposure might be encountered in patients with hepatic impairment. Preliminary data published in an abstract form indicated that exposure to posaconazole (single 200 mg dose of oral suspension) was enhanced by 1.3 fold in 4 patients with severe hepatic dysfunction when compared to that obtained in 4 normal subjects [18]. However, no recommendations regarding an adjustment of dose in patients with hepatic dysfunction have been issued.

FACTORS ALTERING THE PHARMACOKINETICS OF POSACONAZOLE

Food

Given the physico-chemical characteristics of posaconazole (low solubility, high permeability), food, particularly high-fat meal, is expected to increase its intestinal absorption, in relation with an improved solubilization. The effect of food on posaconazole disposition has been studied in 20 healthy volunteers [5]. After a single dose (200 mg) of oral suspension the AUC_{0-72h} of posaconazole, given with a high-fat breakfast, was increased 3.9 fold when compared with that obtained in the fasting state. When given with a nonfat meal, the AUC_{0-72h} of posaconazole increased 2.7 fold [5]. Due to the fact that high-risk patients (those candidate to antifungal prophylaxis) might have difficulties eating

solid food, the effect of a nutritional supplement on posaconazole kinetics has been tested in 24 healthy volunteers [19]. Again, the $AUC_{0\text{-}72h}$ of posaconazole (400 mg, single dose of oral suspension) given with the oral supplement was shown to be increased 2.5 fold when compared to that calculated in the fasted state. Hence, the package insert recommends the intake of posaconazole oral suspension with a meal or a nutritional supplement to ensure optimal exposure.

Dosing schedule

Reducing the dosing interval has been shown to increase exposure. In 18 fasted healthy volunteers, administration of 400 mg (suspension) every 12 hours or 200 mg every 6 h led to 2 fold and 3 fold increases in the posaconazole exposure ($AUC_{0\text{-}48h}$), respectively, when compared to the single daily dose (800 mg) [20]. In an another study including 61 patients, the exposure to posaconazole (oral suspension) was shown to increase 1.8 fold, at steady state, when the daily dose (800 mg) was split in two [21]. Despite its long terminal half-life but in relation with its poor solubility, posaconazole oral suspension has to be given in divided doses.

Age

The pharmacokinetics of posaconazole (400 mg twice a day) has been studied in 24 elderly subjects (65-85 years) [22]. At steady state, the $AUC_{0\text{-}12h}$ was 1.3 fold higher than those obtained in 24 young subjects (18-45 years). Given the high interpatient variability (40% in both groups), the difference was not judged relevant. According to the official labeling, no dose adjustment is needed in elderly patients.

Body weight, body surface area

In young patients (age: 8-17 years; body weight: 24-76 kg), body weight or body surface area did not account for the interindividual variability of plasma concentrations at steady state [17]. In adult patients, body weight did not influence posaconazole exposure at steady state, thus justifying the use of a fixed dose as for other azoles, except voriconazole [21] [22] [23].

Pharmacogenetics

As seen above, posaconazole is transported by P-gp. Some genetic variants for MDR1 (in particular the single-nucleotide polymorphism or SNP C3435T) have been associated with variation of P-gp expression and, therefore, in alterations of pharmacokinetics [24]. No association between C3435T MDR1 genetic variant and exposure to oral posaconazole has been found in 56 subjects [22]. It could mean that variability in intestinal P-gp expression in relation with the variant C3435T has no significant impact on oral absorption of posaconazole.

Other factors

Neither gender nor ethnicity has been shown to influence posaconazole pharmacokinetics [22].

Pharmacodynamics

High interindividual kinetic variability (i.e., coefficient of variation or CV in the 40-80% range regarding AUC) has been reported in patients receiving posaconazole [13] [21]. Higher plasma concentrations of posaconazole have been associated with greater responses rates in 67 patients with invasive aspergillosis and who received the triazole at 800 mg in divided doses [25]. For example, optimal response rate (75%; 12/16 patients) was obtained at an average plasma concentration of 1.25 mg L^{-1}. In high risk patients receiving posaconazole at 200 mg thrice daily as prophylactic treatment, lower plasma concentrations were observed in 4 of 5 patients who developed invasive fungal infection when compared to those of 241 patients without infection (median average concentrations: 0.61 mg L^{-1} vs. 0.92 mg L^{-1}) [23]. As with oral itraconazole, monitoring of plasma concentrations of posaconazole might be warranted to avoid underexposures, although no target values for treatment of invasive fungal infections and prophylaxis are available so far.

DRUG-DRUG INTERACTIONS

Pharmacokinetic interactions commonly occur via drug-metabolizing enzymes or drug transporters. As mentioned earlier, posaconazole is eliminated as unchanged drug, predominantly via biliary excretion. P-gp expressed at luminal side of hepatocytes might mediate transport into the bile. Biotransformation represents a minor route of elimination and is catalyzed by UGT1A4. Theoretically, only non-metabolic interactions are anticipated, for example with inhibitors or inducers (i.e., drugs activating orphan nuclear receptors) of drug transporter expression.

The potential for posaconazole to modify the kinetics of co-administered appears high. As for some of its congeners (itraconazole, ketoconazole), posaconazole is a dual CYP3A4 and P-gp inhibitor. *In vitro*, the IC_{50} regarding CYP3A4 activity for dextromethorphan N-demethylation is 1.3 µM (0.91 mg L^{-1}), in the range of the C_{max} obtained at steady state, after ingestion of the oral suspension (400mg twice daily) but much higher than the un-

bound plasma concentration [26]. *In vivo*, posaconazole (200 mg once daily) increased the AUC of intravenous midazolam (probe drug for CYP3A inhibition) by 1.8 fold [26], meaning that the hepatic unbound concentration of the azole is higher than that determined in plasma and is sufficient to inhibit CYP3A activity (i.e., CYP3A4 and CYP3A5).

Based on current recommendations it is difficult to classify posaconazole as a strong, moderate, or weak CYP3A inhibitor because it has not been tested at its highest dose (i.e., 800 mg) with the oral form of midazolam (more sensitive substrate than the intravenous form) [27]. In addition, the inhibitory potency towards CYP3A5 is not known. Hepatic CYP3A expression is variable in relation, among others, with genetic mutations of CYP3A5. Besides the substrate, the extent of CYP3A inhibition by an azole may vary with the expression of CYP3A5 (in general, low in Caucasians when compared with African Americans) and the respective inhibition potency towards CYP3A4 and CYP3A5 (fluconazole is a more potent inhibitor of CYP3A4 than CYP3A5) [28]. However, and without any kinetic documentation, posaconazole is contraindicated with CYP3A4 substrates whose increased exposure can cause dramatic effects like ergot alkaloids, drugs known to prolong QT interval (quinidine), or some 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., simvastatin, atorvastatin). *In vitro*, posaconazole did not inhibit CYP1A1, CYP2C8/9, CYP2D6, and CYP2E1 [26]. Unlike its congeners, it is not known whether posaconazole interacts as an inhibitor with the transporter breast cancer resistance protein (BCRP or ABCG2) expressed in the intestine and in the liver canalicular membrane. Regarding P-gp, the inhibitory potential of posaconazole has not been described (data from the manufacturer) and does not appear in the product information.

Given the profile of inpatients receiving posaconazole (intensive care units, oncology-hematology units), the interacting drugs of concern are mainly immunosuppressants, anticancer drugs, some analgesics and hypnotics. Most of the studies exploring drug-drug interactions have been performed in healthy volunteers and have been conducted by the manufacturer.

Drugs that potentially increase posaconazole concentrations

Drugs that inhibit P-gp transport (erythromycin, verapamil) might affect posaconazole disposition by enhancing its absorption and/or decreasing its biliary secretion. Currently, no pharmacokinetic data of posaconazole given with a P-gp inhibitor have been reported.

Drugs that potentially decrease posaconazole concentrations

Antiacids

Drugs whose oral absorption is dependent on acid gastric pH like some azoles (ketoconazole, itraconazole) might be affected by antiacids. Coadministration of an aluminium/magnesium containing antiacid did not significantly alter posaconazole absorption in fasting or non-fasting healthy volunteers [29]. In contrast, coadministration of cimetidine (400 mg twice daily), an histamine H_2-receptor antagonist, with posaconazole tablets (200 mg once daily with food) lead to a 40% decrease in azole exposure and C_{max} [30]. The terminal half-life was not affected underlining the likely decrease in absorption. Thus, it is recommended to avoid the association of posaconazole with a histamine H_2-receptor antagonist or proton pump inhibitor.

Rifampin, rifabutin

Rifampin or rifabutin are pleiotropic inducers increasing the expression of enzymes or transporters. They interact with orphan nuclear receptors like pregnane X receptor (PXR or SXR) or constitutive androstane receptor (CAR) that act as transcriptional factors regulating the expression of genes coding for pharmacokinetic determinants [31]. When combined with rifabutin (300 mg once a day for 17 days), the exposure of posaconazole given 200 mg once daily in 24 healthy males decreased by 49%, at steady state [32]. The interaction might be imputable to increased expression of UGT1A4 and P-gp. The interaction with rifampin, considered to be the strongest inducer due to its slower elimination (relative to rifabutin), has not been investigated. According to the package insert, association of posaconazole with rifampin or rifabutin must be avoided.

Phenytoin

Phenytoin is an inducer of human CYP3A4 and CYP2B6 presumably via activation of the nuclear receptors PXR and CAR, respectively [31]. Phenytoin has not been shown to induce expression of known posaconazole kinetic determinants. Surprisingly, data published in an abstract form reported that the apparent clearance of posaconazole (200 mg once a day) increased by 90% in 36 healthy volunteers when combined with phenytoin (200 mg once a day) [33]. The mechanism relative to the increase in posaconazole elimination is currently

unknown. According to the package insert, this association should be avoided.

Drugs kinetics altered by posaconazole

Midazolam

As seen above, posaconazole (200 mg) increased intravenous midazolam exposure 1.8 fold in 12 healthy volunteers, in relation with the CYP3A catalyzed metabolism inhibition of the hypnotic [26][26]. Therefore, dose reduction of midazolam (and benzodiazepines such as alprazolam, triazolam) should be performed while co-administrated with posaconazole.

Tacrolimus

Coadministration of posaconazole (400 mg twice daily for 8 days) and tacrolimus (0.05 mg kg^{-1} day^{-1}) in 36 healthy volunteers lead a 4.2 fold increase in the AUC of the immunosuppressive agent suggesting an inhibition of hepatic biotransformation catalyzed by CYP3A4 and a potential limitation of an intestinal first pass effect involving CYP3A4 and P-gp [34]. It is recommended to decrease tacrolimus dose by 33% when the treatment with posaconazole is initiated. Coadministration of an azole strengthens the monitoring of tacrolimus blood concentrations.

Cyclosporine

Administration of oral posaconazole (200 mg daily) to 4 heart transplant subjects under stabilized oral cyclosporine therapy increased the dose-normalized exposure to the immunosuppressant by 33%, leading to 14-29% reduction of cyclosporine dosage in 3 patients [34]. Cyclosporine-increased exposure is probably related to the inhibition of P-gp and CYP3A4 by posaconazole. Overall, cyclosporine dosage must reduced by 25% at the beginning of treatment with posaconazole. Blood concentrations must be carefully monitored thereafter (as usual).

Vincristine

A severe peripheral neurotoxicity has been reported in a young patient with acute lymphoblastic leukemia who received intravenous vincristine with oral posaconazole [35]. Vincristine is transported by P-gp and its metabolism was recently (2006) shown to be catalyzed by CYP3A4 and CYP3A5 [36]. Although the pharmacokinetics of vincristine was not investigated, posaconazole might have delayed the elimination of the anticancer drug. Thus, the association of posaconazole with Catharanthus ('vinca') alkaloids (vinblastine, vincristine, vinorelbine) is not recommended.

CONCLUSIONS

Posaconazole pharmacokinetic profile is characterized by a saturated oral absorption when daily dosage exceeds 800 mg, in relation with its lipophilicity and an unknown absolute bioavailability due to the lack of intravenous kinetic data. In corollary, the systemic clearance is undetermined. Drug exposure increases with repeated administration and is optimized when the antifungal agent is given with food or an oral supplement, in divided doses, regardless of its long terminal half-life. Association of posaconazole with orphan nuclear receptors interacting drugs ("inducers") must be avoided because it can lead to therapeutic failures. In addition, posaconazole has the potential to alter the pharmacokinetics of co-administered drugs in relation with the inhibition of P-gp drug transport and/or CYP3A4 activity. Several significant interactions have been reported and numerous others are suspected (digoxin, sirolimus).

AUTHORS' PARTICIPATION

D L designed the paper, collaborated in the first draft and reviewed final version of the manuscript. YN helped to analyze the information and collaborated in the first draft. F J and G U-S reviewed the final paper. R H helped to analyze the information and reviewed the final version of the manuscript.

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CONFLICT OF INTERESTS/DISCLAIMERS

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