No clinically significant pharmacokinetic interactions between voriconazole and indinavir in healthy volunteers

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Aims Voriconazole is a new triazole antifungal agent, and is metabolized by the cytochrome P450 isoenzymes CYP2C9, CYP2C19 and to a lesser extent by CYP3A4. Protease inhibitors, such as indinavir, are also metabolized by cytochrome P450 (mainly CYP3A4). As these drugs are likely to be coadministered, these studies were performed to assess the pharmacokinetic interactions, safety and toleration of these drugs when taken together.

Methods Two randomized placebo-controlled studies were conducted in healthy male volunteers. Study A was an open parallel-group study of the effect of indinavir on the steady-state pharmacokinetics of voriconazole in 18 volunteers (nine subjects in each group). Subjects received voriconazole 200 mg twice daily (days 1–7), then voriconazole 200 mg twice daily + indinavir 800 mg or placebo three times daily (days 8–17). Study B was a double-blind, randomized, two-way crossover study of the effect of voriconazole on the steady-state pharmacokinetics of indinavir in 14 volunteers. They received indinavir 800 mg three times daily + voriconazole 200 mg or placebo twice daily for two 7-day treatment periods separated by a washout period of at least 7 days. Pharmacokinetic parameters were compared within treatment groups at days 7 and 17 in Study A and between treatment groups on day 7 of each period in Study B. All adverse events were recorded.

Results Study A: Seventeen subjects were evaluable for pharmacokinetic analysis (eight voriconazole + indinavir, nine voriconazole + placebo). The day 17/day 7 ratios for C_{max} and AUC_{τ} were estimated as 102% [90% confidence interval (CI) 91, 114] and 107% (90% CI 98, 118), respectively. Study B: Fourteen subjects were evaluable for pharmacokinetic analysis in each treatment period. The ratios between the geometric means for indinavir + voriconazole *vs.* indinavir + placebo were: C_{max} , 91% (90% CI 83, 101), AUC_{τ} , 87% (90% CI 77, 100), and C_{min} , 101% (90% CI 82, 125). Trough plasma concentrations of indinavir were above the concentration required to inhibit HIV replication (IC_{95}) in both treatment periods. Voriconazole coadministered with indinavir was well tolerated in both studies.

Conclusions The coadministration of voriconazole and indinavir in healthy volunteers had no clinically significant effect on the pharmacokinetics of either voriconazole or indinavir.

Keywords: indinavir, pharmacokinetics, voriconazole

Introduction

Voriconazole is a new triazole antifungal agent, developed as oral and intravenous formulations, with potent activity against a broad spectrum of clinically significant pathogens, including *Aspergillus* and *Candida* species [1–

3], and emerging fungal pathogens, such as *Scedosporium* and *Fusarium* species [4, 5].

The pharmacokinetics of voriconazole have been investigated following single and multiple (7–30 days) doses in both healthy volunteers and patients [6–8]. Voriconazole is extensively metabolized by the cytochrome (CYP) P450 system, mainly by the polymorphically expressed CYP2C19 isoenzyme, by CYP2C9, and to a lesser extent by CYP3A4 [9].

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Indinavir is a protease inhibitor that is widely used in the management of HIV/AIDS. A number of clinical trials have demonstrated its efficacy in combination with other antiretroviral therapies, and HIV protease inhibitor-based regimens are recommended as first-line options in British and American treatment guidelines [10, 11]. Available protease inhibitors, including indinavir, are, like voriconazole, metabolized by the cytochrome P450 system (mostly by CYP3A4) [12].

The likelihood of coadministration of voriconazole and indinavir is expected to be high, because patients with AIDS are highly susceptible to serious opportunistic fungal infections. Since CYP3A4 is at least partly involved in the metabolism of both agents, alterations in the pharmacokinetic profiles of voriconazole and/or indinavir may occur if they are administered together. As a patient group, HIV/AIDS patients are routinely given a large number of medications in addition to protease inhibitors, many of which are also metabolized by CYP3A4. Thus, the potential for drug interactions in these patients is high.

The two studies reported here were designed to investigate the pharmacokinetic interactions, safety, and toleration of voriconazole and indinavir when coadministered.

Methods

Subjects

Healthy male volunteers aged 18–45 years, weighing between 60 and 100 kg, and with a body mass index between 18 and 28 according to Quetelet's Index [$\text{weight}(\text{kg})/\text{height}^2(\text{m})$] were eligible for inclusion in the studies.

Volunteers were excluded if they had laboratory or physical abnormalities, or a history of clinically significant allergies, especially to medical treatments.

Both studies were approved by appropriate ethics review committees (Clinical Research Ethics Committee, Anatole France Street, Brussels, Belgium; Canterbury Research Ethics Committee, Canterbury, UK), and all subjects gave written informed consent prior to enrolment.

Study design

Study A was an open, randomized, placebo-controlled, parallel-group study. Study B was a double-blind, randomized, placebo-controlled, two-way crossover study.

In the 3 weeks prior to the start of each study, a screening visit was conducted, which included physical and ophthalmological examinations, measurement of supine blood pressure and pulse, and a 12-lead electro-

cardiogram (ECG). In addition, blood samples for routine haematological and biochemical testing, and urine for urinalysis and drug screening, were obtained. These examinations were repeated for subjects in both studies 7–10 days after receiving the final dose of study drug.

Drug administration

Study A All subjects received voriconazole 200 mg twice daily on days 1–17 of the study. In addition, they were randomized to receive either indinavir 800 mg three times daily (indinavir group), or placebo three times daily (placebo group) on days 8 through 17 of the study. Subjects were admitted to the unit on the day prior to the first dosing day, and a physical examination, urine screening for drugs of abuse and a breath alcohol test were performed. The subjects were resident in the unit until 2 h postdose on the morning of day 1. Subjects were required to attend the unit every morning on days 2 through 6 to receive their voriconazole doses. They then remained resident in the unit from the evening of day 6 until the morning of day 18.

Study B Subjects were randomized to receive study drugs for two periods of 7 days each, separated by a washout period of at least 7 days. Depending on the randomization, eight subjects received treatment according to the sequence: indinavir 800 mg three times daily plus voriconazole 200 mg twice daily followed by indinavir 800 mg three times daily plus placebo (voriconazole/placebo group), and the other eight subjects received indinavir 800 mg three times daily plus placebo followed by indinavir 800 mg three times daily plus voriconazole 200 mg twice daily (placebo/voriconazole group). Subjects were admitted to the unit on the evening prior to the first day of dosing and remained resident until the morning of day 8 of each study period. In both studies, voriconazole and indinavir were not taken less than 1 h before or 2 h after food.

Safety analysis

In both studies, safety was assessed by recording adverse events, and by evaluating the subjects' physical examinations and laboratory test data. Investigators recorded the relationships of adverse events to study drug. Reasons for any withdrawals from the studies were also recorded.

Pharmacokinetic sampling

In Study A, blood samples for the measurement of plasma voriconazole concentrations were collected before dosing on days 2–6, 8–16 and day 18. In addi-

tion, on days 7 and 17 blood samples were collected before voriconazole administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after dosing. In Study B, blood samples for the measurement of plasma indinavir concentrations were taken prior to the morning dose on days 1–6 of each treatment period. In addition, on day 7, blood samples were collected before indinavir administration and at 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 h after dosing.

In both studies, all samples for study drug analyses were collected into heparinized tubes and centrifuged within 1 h of collection at 1500 g, 4 °C for 10 min. The plasma was decanted and stored at –20 °C in screw-capped polypropylene tubes prior to analysis.

Assays

Plasma voriconazole levels were determined using a previously validated high-performance liquid chromatography (HPLC) method [13] [Huntingdon Life Sciences, Huntingdon, UK (Study A); BAS Analytics Ltd, Kenilworth, UK (Study B)]. Interbatch imprecision and inaccuracy of the assay were in the ranges 5.0–10.1% and –3.5–0.4%, respectively, over the range 25–2500 ng mL^{–1} (Study A); and 3.98–7.97% and 2.44–9.20%, respectively, over the range 25–2503 ng mL^{–1} (Study B). The assay was validated over the concentration range 10–3000 ng mL^{–1}, with a 0.9% imprecision at the lowest level (Study A). The limit of quantification was 10 ng mL^{–1} in both studies.

Plasma indinavir concentrations were determined using an HPLC method (KeyStone Analytical Laboratories, Inc., North Wales, PA, USA). Back-calculated calibrator concentrations demonstrated imprecision and inaccuracy ranging from 2.70 to 5.77% and –6.89 to 7.20%, respectively, over the range 25–2000 ng mL^{–1} (Study A), and the interbatch imprecision ranged from 5.80 to 8.80% over the range 75–2800 ng mL^{–1} (Study B). In Study B, the inaccuracy of the assay at all concentrations ranged from –3.07 to 1.43%. The limit of quantification was 25 ng mL^{–1}.

Parameter calculations

The following pharmacokinetic parameters were determined for voriconazole (Study A) and indinavir (Study B): AUC_τ (ng·h mL^{–1}), the area under the plasma concentration–time curve within the dosing interval, using the linear trapezoidal rule; C_{max} (ng mL^{–1}), the maximum observed plasma concentration, and t_{max} (h), the time to first occurrence of C_{max}, both taken from the recorded plasma concentration–time data. In Study B, the following additional parameters were determined for indinavir: k_{el} (h^{–1}), the terminal phase elimination rate constant, by

log-linear regression on those points visually assessed to be on the terminal log-linear phase; CL/F (l h^{–1}), the apparent oral clearance, as dose/AUC; and t_{1/2}, the terminal elimination half-life, as 0.693/k_{el}.

Statistical analysis

A sample size of 16 subjects for Study A was considered sufficient to detect a difference of 30% between day 17 and day 7 for AUC_τ and C_{max} with at least 80% power when testing (two-sided) at the 5% level. The estimate of variability was based on results from a previous study (Data on file, Pfizer Inc.). In Study B, a sample size of 14 subjects was considered sufficient to detect a difference of at least 25% between study drug groups in AUC_τ and C_{max} with 80% power when testing (two-sided) at the 5% level. The estimate of variability was based on published results [14].

In both studies, log-transformed AUC_τ, log-transformed C_{max}, and untransformed t_{max} were subjected to analysis of variance (ANOVA) appropriate for the study design. In Study A the ANOVA allowed for variability due to treatment group, subject, day, and the day by treatment group interaction. The mean differences day 17–day 7 were estimated for each treatment group and then these differences were compared between treatment groups. Ninety percent confidence intervals (CI) were calculated for each comparison. In Study B the ANOVA allowed for variability due to sequence, subject within sequence, period, and treatment. The mean differences between treatments were estimated along with their 90% CI. In Study B, log-transformed CL/F and untransformed k_{el} were also analysed. In both studies, the ratio between antilogged treatment means and the corresponding antilogged CIs were presented for AUC_τ and C_{max}.

Results

Subjects

Study A Eighteen subjects were enrolled and randomized to receive study drug. Baseline demographics were similar between the two groups (Table 1). One subject withdrew from treatment on day 10, thus 17 subjects completed the study.

Study B Sixteen subjects were enrolled in the study and randomized to receive study drug (eight in each sequence group). There were no significant baseline demographic differences between sequence groups (Table 1). Two subjects withdrew from the study during the indinavir + placebo period. Data from 14 subjects were evaluable for pharmacokinetic analysis.

Table 1 Baseline demographic characteristics of all randomized subjects.

	Study A		Study B	
	Voriconazole + indinavir	Voriconazole + placebo	Indinavir + voriconazole → indinavir + placebo	Indinavir + placebo → indinavir + voriconazole
Number of subjects	9	9	8	8
Mean age, years (range)	25 (19–37)	22 (19–25)	31 (22–45)	31 (20–41)
Mean weight, kg (range)	71 (61–85)	74 (67–91)	73 (64–86)	76 (62–98)
Mean height, cm (range)	181 (173–197)	177 (168–192)	176 (169–187)	178 (168–187)

Table 2 Summary of mean pharmacokinetic parameters for voriconazole in plasma (Study A).

Parameter	Voriconazole + indinavir (V + I)			Voriconazole + placebo (V + P)			V + I vs. V + P
	Means		Difference/ratio between means★ (90% CI)	Means		Difference/ratio between means★ (90% CI)	Difference/ratio between means★ (90% CI)
	Day 7	Day 17		Day 7	Day 17		
C _{max} (ng ml ⁻¹)†	1745	1724	99% (91, 107)	2 235	2 165	97% (90, 105)	102% (91, 114)
AUC _τ (ng·h ml ⁻¹)†	8706	8779	101% (94, 108)	12 846	12 075	94% (87, 100)	107% (98, 118)
t _{max} (h)‡	1.7	1.8	0.1 (− 0.3, 0.4)	1.7	1.7	0.0 (− 0.3, 0.3)	0.1 (− 0.4, 0.5)

*Ratio (%) between means shown for $C_{\max}$ and AUC_{τ} , difference between means for $t_{\max}$. †Geometric mean. ‡Arithmetic mean.

Figure 1 Mean plasma concentrations of voriconazole in Study A (days 7 and 17).

Pharmacokinetics

Study A Both study groups achieved steady-state plasma voriconazole levels by day 6. Pharmacokinetic results are shown in Table 2. The ratios between the geometric means of voriconazole $C_{\max}$ and AUC_{τ} for the voriconazole + indinavir group were 99% and 101%, respectively. For the voriconazole + placebo group, the values were 97% and 94%, respectively. Comparing the two treatment groups, the $C_{\max}$ and AUC_{τ} ratios were 102% (90% CI 91, 114) and 107% (90% CI 98, 118), respectively. The differences between the day 17 and day 7 arithmetic

means of voriconazole $t_{\max}$ were 0.1 h for the voriconazole + indinavir group and 0.0 h for the voriconazole + placebo group. The mean plasma concentrations of voriconazole were similar when voriconazole was given alone (day 7) to when it was coadministered with either indinavir or placebo (day 17), although mean concentrations were generally higher for the voriconazole + placebo group than for the voriconazole + indinavir group for both days (Figure 1).

Study B The ratios between the geometric means of indinavir $C_{\max}$ and AUC_{τ} between the indinavir + vori-

conazole and the indinavir + placebo treatments were 91% (90% CI 83, 101) and 87% (90% CI 77, 100), respectively. $t_{\max}$ was not formally analysed as each subject reported identical results on both treatments (arithmetic mean of 1.1 h for both treatments). The difference between the arithmetic means of k_{el} was -0.036 h, and the ratio between the geometric means of CL/F was 114%. Pharmacokinetic results are shown in Table 3. The mean plasma concentrations of indinavir on day 7 were similar when coadministered with either voriconazole or placebo (Figure 2).

Safety

Study A There were no serious adverse events reported in either group. In the voriconazole + indinavir group, six of nine subjects reported 14 study drug-related

adverse events; in the voriconazole + placebo group, four of nine subjects reported four events. One subject withdrew from the voriconazole + indinavir group on day 10 of the study as a result of study drug-related digestive adverse events (classified as severe abdominal pain, severe nausea, severe halitosis, moderate vomiting). These events subsequently resolved without intervention.

Two subjects in the voriconazole + indinavir group, and three in the voriconazole + placebo group, reported visual adverse events that were considered related to study drug. These events (occasional luminous flashes, blurred vision, dazzling) were all mild in intensity, intermittent and of short duration, and all resolved without further action.

Study B Seventeen study drug-related adverse events were reported by nine of 14 subjects in the indinavir + voriconazole administration period, and 11 events by five of 16 subjects in the indinavir + placebo period. The majority of these were classified as mild or moderate in intensity (only two were classified as severe: headache and nausea, each in one subject during the indinavir + voriconazole period).

Visual adverse events (visual disturbance, photophobia) were reported by three subjects during the indinavir + voriconazole period, and by two in the indinavir + placebo period. Four of these events were assessed as mild in intensity, one as moderate; they all resolved without intervention.

Two subjects were withdrawn from the study whilst receiving indinavir + placebo. One withdrawal was due to study drug-related abnormal laboratory parameters (elevated liver enzymes), which had returned to normal at follow-up, and one was due to an inflamed cyst not regarded as treatment-related, but which was reported as a severe adverse event.

Table 3 Summary of mean indinavir pharmacokinetic parameters in plasma (Study B).

Parameter	Indinavir + voriconazole, mean	Indinavir + placebo, mean	Difference/ratio between means* (90% CI)
$C_{\max}$ (ng mL ⁻¹)†	7 323	8 017	91.4% (82.7, 101)
$C_{\min}$ (ng mL ⁻¹)†	99	98	101% (82.1, 125)
AUC_{τ} (ng·h mL ⁻¹)†	16 266	18 594	87.5% (76.7, 99.8)
CL/F (L h ⁻¹)†	49	43	114% (100, 130)
k_{el} (h ⁻¹)‡	0.527	0.563	-0.036 ($-0.073, 0.001$)

*Ratio (%) between means shown for $C_{\max}$, AUC_{τ} , and CL/F , difference between means for k_{el} . †Geometric mean. ‡Arithmetic mean.

Figure 2 Mean plasma concentrations of indinavir in Study B (day 7).

Discussion

These studies are the first to investigate the potential pharmacokinetic effects of voriconazole and indinavir coadministration. The results show no clinically significant alterations in the pharmacokinetics of either agent as a result of coadministration.

In Study A, voriconazole $C_{\max}$ and AUC_{τ} were approximately 2% (90% CI -9, 14) and 7% (90% CI -2, 18) higher when coadministered with indinavir, respectively, compared with placebo. The similarity in $t_{\max}$ data between the two groups shows that indinavir did not affect the rate at which voriconazole $C_{\max}$ was achieved. In Study B, indinavir $C_{\max}$ was 9% (90% CI -1, 17) lower when administered with voriconazole compared with placebo, and the AUC_{τ} was 13% (90% CI 0, 23) lower. Indinavir $C_{\min}$, defined as the plasma concentration 8 h after the morning dose on day 7, was 1% (90% CI -18, 25) higher when coadministered with voriconazole. In both treatment periods, the ranges of trough ($C_{\min}$) indinavir concentrations (indinavir + voriconazole 42–212 ng mL⁻¹, indinavir + placebo 53–254 ng mL⁻¹) were noted to be above the American Society of Health-System Pharmacists' definition of the concentration required to inhibit 95% of HIV replication *in vitro* (IC₉₅) of approximately 16–67 ng mL⁻¹ (25–100 nM). Furthermore, indinavir $C_{\min}$ concentrations were above the minimum effective concentration range of 60–100 ng mL⁻¹ (97–160 nM) suggested by other researchers for 10 out of 14 subjects in the indinavir + voriconazole treatment period and 11 out of 14 subjects in the indinavir + placebo period [15]. Hence, the therapeutic outcome of indinavir therapy is considered unlikely to be affected by concomitant voriconazole administration. Values for indinavir $t_{\max}$ were identical between the two treatment groups, and mean values were similar for the indinavir k_{el} . Mean indinavir CL/F was observed to be 14% (90% CI 0, 30) higher when indinavir was coadministered with voriconazole.

The dose of indinavir that was used in these studies is the currently approved recommended dose. However, it is recognized that it is now common practice to administer indinavir in combination with low-dose zidovudine in order to boost the plasma concentration of indinavir [16]. Twice-daily administration to volunteers of 800 mg indinavir and 100 mg zidovudine with food for 2 weeks resulted in indinavir AUC_{24} increases of 178% compared with historical AUC_{24} values for patients who received indinavir 800 mg every 8 h alone [17]. Thus, the overall exposure of patients to indinavir in current clinical practice may be greater than that observed in Study A.

The combination of voriconazole and indinavir in both studies was well tolerated. There were only two study drug-related withdrawals, one from the voriconazole + indinavir group in Study A, and one from the indinavir + placebo group in Study B.

zole + indinavir group in Study A, and one from the indinavir + placebo group in Study B.

Although both voriconazole and indinavir are metabolized by the cytochrome P450 enzyme system, they predominantly involve different isoenzymes. Voriconazole is mainly metabolized by CYP2C9 and CYP2C19 [9], whereas protease inhibitors, such as indinavir, are metabolized mainly by CYP3A4 [12, 18, 19]. Therefore, our finding that there are no clinically significant interactions between voriconazole and indinavir may have been predicted.

Although this healthy volunteer study provides no direct evidence of how voriconazole and indinavir may interact in patients with HIV/AIDS, the likelihood of a clinical interaction is probably low, given the reassuring data available for the first-generation triazole, fluconazole in this setting [19].

The current study suggests that voriconazole and indinavir can safely be coadministered without the need for dose adjustment of either drug.

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