

Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults

Rachel Courtney,¹ David Wexler,² Elaine Radwanski,³ Josephine Lim² & Mark Laughlin¹

¹Early Clinical Research and Experimental Medicine, ²Drug Metabolism and Pharmacokinetics and ³Project Planning, Schering-Plough Research Institute, Kenilworth, New Jersey, USA

Correspondence

Rachel Courtney, PhD, Early Clinical Research and Experimental Medicine, Schering-Plough Research Institute, K-15-4-4455, 2015 Galloping Hill Road, Kenilworth NJ, 07033, USA.
Tel: +1 90 8740 3836
Fax: +1 90 8740 2916
E-mail: rachel.courtney@spcorp.com

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Aims

This randomized, crossover, single-dose study evaluated the relative oral bioavailability of posaconazole suspension and coprecipitate tablet formulations. Additionally, the study determined whether systemic exposure to posaconazole was affected by prandial status or by the fat content of a meal.

Methods

This was a randomized, open-label, four-way crossover, single-dose study in 20 healthy men. Posaconazole pharmacokinetics were evaluated over 72 h following a single oral dose of posaconazole suspension (200 mg/5 ml) administered with a high-fat meal, a nonfat breakfast, or after a 10 h fast, or posaconazole tablets (2 × 100 mg) administered with a high-fat meal.

Results

The posaconazole suspension showed a significant increase in bioavailability compared with the tablet (increase in AUC(0,72 h) = 137% (90% confidence interval (CI) 119%, 156% and C_{max} = 123% (90% CI 104%, 146%). The mean increases in AUC(0,72 h) and C_{max} values were about 400% when administered with a high-fat meal compared with administration of the suspension in the fasting state (AUC(0,72 h) 90% CI 343%, 448%; C_{max} 90% CI 352%, 493%). Administration of the suspension with a nonfat meal enhanced exposure, resulting in an increase in AUC(0,72 h) of 264% (90% CI 231%, 302%) and in C_{max} of 296% (90% CI 250%, 350%) relative to the fasted state.

Conclusions

The suspension formulation of posaconazole was associated with enhanced systemic exposure and increased relative bioavailability compared with the tablet. Food substantially enhanced the rate and extent of posaconazole absorption in healthy subjects.

Introduction

Posaconazole is a potent, broad-spectrum, triazole antifungal agent, currently in clinical development for the treatment of refractory invasive mycoses [1–8]. Initial clinical efficacy data suggest that posaconazole is an effective and well-tolerated treatment in infections due to zygomycetes, *Aspergillus* and *Fusarium* [9].

Prandial status has differing effects on the bioavailability of the marketed triazole antifungals. Relative to the fasted state, a high-fat meal decreased voriconazole C_{max} and AUC(0,72 h) values by 34% and 24%, respectively [10]. The absorption of itraconazole capsules is doubled when given postprandially [11, 12], possibly because of increased gastric residence time and

improved dissolution. As posaconazole is a highly lipophilic base ($\log P > 3$, pK_a 3.6 and 4.6) of similar molecular weight to itraconazole ($\log P = 5.66$, pK_a 3.7), its bioavailability was also expected to be greater in the fed state. Unlike itraconazole, most of a posaconazole dose is excreted unchanged in the faeces, so the effects of food on intestinal and hepatic metabolic enzymes were expected to be minimal [13].

As a tablet formulation, posaconazole exhibits dose-proportional kinetics after single-dose (50 mg–800 mg) and multiple-dose regimens (50 mg–400 mg twice daily for 14 days) [14]. Owing to the potential dissolution limitation of posaconazole, and to enhance its exposure, the relative oral bioavailability of a suspension compared with the tablet formulation of posaconazole was evaluated with a high-fat meal. To determine if food and its fat content influenced bioavailability, we studied the systemic exposure to posaconazole oral suspension when given in the fasted state and after a non-fat meal.

Methods

Subjects

Healthy adult men aged 18–45 years, within 15% of ideal body weight and in good health were enrolled. The protocol was approved by the Medical Ethics Committee of the 'Landesärztekammer Baden-Wuerttemberg' in Stuttgart, Germany. Each subject was required to provide written informed consent before enrolment. The study was conducted in accordance with the Declaration of Helsinki.

Study design

Subjects were randomly assigned in a crossover manner to receive posaconazole suspension (200 mg/5 ml) with a high-fat breakfast (841 calories, 52% fat), or a nonfat breakfast (461 calories, 0% fat), or after a 10 h fast, or 2100 mg posaconazole tablets, with the high-fat breakfast. Except for acetaminophen, no concomitant drugs were permitted.

All meals were consumed within a 20-min period and were followed within 5 min by the assigned treatment. For fasted subjects, water was permitted *ad libitum* until the 4 h postdose blood sample, after which a standardized lunch was provided. For each treatment phase, subjects were confined to the clinic for at least 48 h. They then returned to the clinic for a 72 h postdose evaluation.

Safety

Safety was assessed via physical examinations, ECGs, vital signs, and clinical laboratory tests conducted at

screening, before dosing at each treatment period, and at the conclusion of the study. Additional ECGs were obtained 5 h postdose ($-t_{max}$) during each treatment period. Adverse events were assessed by the investigator for severity and relationship to treatment.

Sample collection and drug analysis

Following each treatment, blood was collected predose (0 h) and at regular intervals up to 72 h postdose. Samples were centrifuged, and the plasma was analysed using a validated high-performance liquid chromatographic assay with ultraviolet detection (262 nm). Cyclobenzaprine hydrochloride was the internal standard and sample cleanup was performed by liquid-liquid extraction. Chromatographic separation was accomplished on an Inertsil ODS-2 column using a mixture of ammonium phosphate buffer, acetonitrile, dichloromethane and triethylamine as the mobile phase. The method was linear over a concentration range of 5–5000 ng ml⁻¹. The mean within-run coefficient of variation (CV) was below 8.1% and the mean between-run CV was below 11.7%. The per cent bias ranged from -3.2–3.4. Recovery for the internal standard was 86% at the concentration used in the assay. Posaconazole was stable in frozen human plasma for at least six months and after three freeze-thaw cycles.

Pharmacokinetic analysis

Individual plasma concentration-time data were used to calculate pharmacokinetic parameters using model-independent methods [15]. The C_{max} and the time to reach the maximum plasma concentration (t_{max}) were the observed values. The area under the concentration-time curve from time 0 h to the final measurable sample (AUC(0,72 h)) was calculated using the linear trapezoidal method. The elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/k$, where k is the negative gradient of the log-linear terminal portion of the plasma concentration-time curve determined using linear regression.

Statistical analysis

The pharmacokinetic parameters were statistically analysed using a crossover analysis of variance (ANOVA) model. The effects due to subject, period, and treatment were extracted. The relative bioavailability of posaconazole, based on the log-transformed AUC(0,72 h) and C_{max} values, was expressed as the ratio of the two treatments. The primary comparisons were: (1) suspension relative to the tablet (following a high-fat meal), (2) suspension (high-fat meal) relative to the suspension (fasted), and (3) suspension (nonfat meal) relative to the suspension (fasted). Ninety per cent confidence intervals

(CIs) for the estimates of bioavailability and the power to detect a 20% difference between treatment means for an α level of 0.05 (two-tailed test) were calculated using the pooled residual error and associated degrees of freedom from the ANOVA.

Results

Subject demographics

Twenty healthy men enrolled in the study. All were white and ranged in age from 22 to 45 years. All subjects completed the treatments and were included in the pharmacokinetic and safety analyses.

Posaconazole pharmacokinetics

Postprandial posaconazole exposure was greater when administered as a suspension than as a tablet formulation (Table 1 and Figure 1). Compared with the tablet formulation, the oral suspension increased mean posaconazole AUC(0,72 h) by 37% (relative AUC(0,72 h) = 137%; 90% CI 119%, 156%; $P = 0.001$) and C_{\max} values by 23% (relative AUC(0,72 h) = 123%; 90% CI 104%, 146%; $P = 0.004$). All but two of the 20 subjects had increased systemic exposure to posaconazole with the suspension vs the tablet formulation.

Mean AUC(0,72 h) and C_{\max} values of posaconazole suspension were four-fold greater when administered with a high-fat meal than when administered while fasted (AUC(0,72 h) 90% CI 343%, 448%; C_{\max} 90% CI 352%, 493%; both $P < 0.001$) (Table 1). Administration of posaconazole suspension with a nonfat meal also enhanced exposure, with mean AUC(0,72 h) and C_{\max} values 2.6-fold (90% CI 231%, 302%) and three-fold (90% CI 250%, 350%) greater than the fasted state, respectively (both $P < 0.001$).

Posaconazole was orally bioavailable, with mean t_{\max} values ranging from 4.1 to 5.5 h for both the suspension and tablet formulations. To account for an outlier in the fasted state, a corrected mean t_{\max} of 3.4 h was calculated, indicating that food slightly decreases the rate of posaconazole absorption. For all treatment regimens regardless of formulation and food intake, the $t_{1/2}$ of posaconazole was approximately 22 h.

Safety

Nine of the 20 subjects reported one or more adverse event. Headache and fatigue, each reported by four subjects, were the most common. Most events were mild and not considered related to the study drug or to the

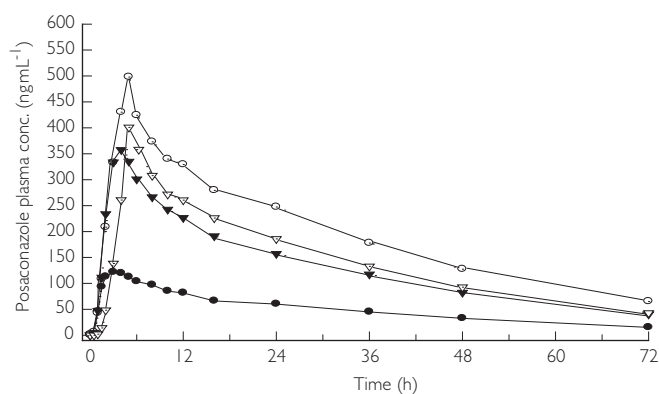


Figure 1

Mean plasma posaconazole concentration-time profiles following single oral administration of 2×100 mg tablets with a high-fat breakfast, and posaconazole suspension (200 mg) following a 10 h fast, a nonfat breakfast, and a high-fat breakfast. Suspension (Fasted) (●), suspension (High-Fat Meal) (○), suspension (Non-Fat Meal) (▼) and tablet (High-Fat Meal) (▽)

Table 1

Mean (% CV) pharmacokinetic parameters of posaconazole following administration of the four regimens

Parameter	Suspension High-fat meal (n = 20)	Tablets High-fat meal (n = 20)	Suspension Nonfat meal (n = 20)	Suspension Fasted (n = 20)
C_{\max} (ng mL ⁻¹)	512 ^{ab} (34)	413 (33)	378 ^b (43)	132 (50)
t_{\max} (h)	4.8 (9)	5.5 (32)	4.1 (21)	5.0 ^c (149)
AUC(0,72 h) (ng mL ⁻¹ h)	13885 ^{bd} (41)	10304 (41)	9511 ^b (38)	3553 (36)
$t_{1/2}$ (h) ^e	23.0 (19)	21.0 (15)	22.2 (18)	23.5 (25)

All data presented as arithmetic means. ^a $P = 0.004$ vs tablets; ^b $P < 0.001$ vs fasted; ^cUsing a t_{\max} of 4 h for one subject, the mean (% CV) t_{\max} is 3.4 (42) h; ^d $P = 0.001$ vs tablets. ^e $n = 15$ for the balanced mean.

plasma posaconazole concentration. However, one subject reported gingivitis, which was moderate in severity. Routine laboratory test results were within normal limits, and no clinically relevant changes in ECGs were observed.

Discussion

Improvements in formulation design account for the greater bioavailability of the posaconazole suspension relative to the tablet formulation in the fed state. The finely divided, wetted dispersed phase of the suspension enables immediate dissolution because of the greater surface area and enhanced gastric mixing of the drug. Based on AUC(0,72 h), a nonfat and high-fat meal enhanced the relative oral bioavailability of the posaconazole suspension by 168% and 290%, respectively, without significantly affecting the rate of absorption. Its pharmacokinetic profile given with a nonfat meal was similar to that of the tablet given with a fatty meal. This suggests that the coadministration of food, regardless of fat content, as well as the administration of the suspension formulation, are the most important factors governing enhanced posaconazole exposure.

A fatty meal provides an ideal oily solvent to solubilize posaconazole into a monomeric, absorbable form. High fat meals also prolong gastric residence times, increasing the amount of the drug mixing with the contents of the stomach and thus the time to absorb the drug.

The effect of food on posaconazole pharmacokinetics was directionally the same as that for itraconazole [11, 12]. However, the magnitude of the effect was twice as great with the posaconazole suspension as with itraconazole capsules [11, 12]. Posaconazole also has a more consistent pharmacokinetic profile than itraconazole, which is associated with erratic absorption. Again, these differences in absorption are probably due to the formulation-derived dissolution profile of each drug, a prerequisite for absorption. However, physiological fluctuations in gastric pH may exert a modest differential effect on the absorption of these antifungal agents. Since itraconazole is a weaker base than posaconazole, its solubility in the stomach after small elevations in pH will be markedly less. Apart from a conserved triazole ring system, voriconazole has a markedly different molecular structure than posaconazole and itraconazole [16], explaining the contrasting effects of food on the absorption of these antifungal drugs.

Most of the adverse events observed in this study were not considered to be related to posaconazole. As no trend was observed between adverse events and plasma posaconazole concentrations, concomitant food

intake with the drug should not be a contra-indication. Ongoing trials will ultimately establish the safety and tolerability profile of posaconazole.

The suspension formulation maximizes the systemic exposure to posaconazole and is more convenient to administer than the tablet, especially in cachectic patients with feeding tubes or those who have difficulty swallowing. Based on these data, the suspension rather than the tablet formulation is currently being evaluated in clinical efficacy trials. Therefore, to ensure optimal absorption, posaconazole should be administered with food or a nutritional supplement (preferably containing fat) whenever possible.

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