Pharmacokinetics of Posaconazole Coadministered with Antacid in Fasting or Nonfasting Healthy Men

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Received 7 April 2003/Returned for modification 6 September 2003/Accepted 18 November 2003

Posaconazole is a potent broad-spectrum azole antifungal agent in clinical development for the treatment of invasive fungal infections. This study evaluated the potential for a pH-dependent pharmacokinetic interaction between posaconazole and an antacid (Mylanta), under fasting and nonfasting conditions. Twelve men completed this randomized, four-period crossover, single-dose study. Subjects received 200 mg of posaconazole following a 10-h fast, with 20 ml of Mylanta and a 10-h fast, with 20 ml of Mylanta and a high-fat breakfast, and with a high-fat breakfast alone. Antacid coadministration had no statistically significant effects on posaconazole bioavailability under fasting or nonfasting conditions. In the fasting state, antacid slightly increased the relative oral bioavailability of posaconazole by 15% ($P = 0.296$); in the nonfasting state, antacid decreased the relative bioavailability of posaconazole by 12% ($P = 0.352$). Food increased the relative oral bioavailability of posaconazole by 400% ($P = 0.001$). In conclusion, the effect of antacid on posaconazole exposure in the fasting or nonfasting state was small and is not considered clinically significant.

Fungal infections are a major cause of morbidity and mortality in neutropenic oncology patients (13, 29, 30), solid organ transplant recipients (23), and persons with AIDS (20). Once thought to be a complication limited to patients with advanced immunodeficiency, mycoses are becoming more common in patient populations not previously considered to be at high risk. For example, surgical patients in intensive care units are acquiring fungal infections with increasing frequency (22, 27). Although Candida and Aspergillus species remain the principal causes of most fungal infections, mycoses due to more unusual fungal pathogens have become more prevalent in recent years. The shifting epidemiology of opportunistic fungal infections, combined with the emergence of pathogenic strains resistant to standard antifungal therapy, has limited present treatment options and underscores the need for the development of new, broad-spectrum agents.

Posaconazole is a new triazole antifungal compound currently in clinical development for the treatment and prophylaxis of invasive fungal infections. Posaconazole exhibits potent and broad-spectrum in vitro activity against a number of common, rare, and emerging fungal pathogens. In addition to being effective in vitro against non-albicans Candida species, Aspergillus species, and Cryptococcus neoformans, posaconazole demonstrates excellent in vitro antifungal activity against Zygomycetes, Basidiomycetes, Scedosporium, Coccidioides, Histoplasma, and Fusarium species (1, 6, 12, 19, 21, 24, 25, 26).

Recent clinical trials have evaluated the pharmacokinetics of posaconazole in healthy volunteers. Following oral administration of rising single or multiple doses given with food, posaconazole exposure (area under the concentration-time curve [AUC]) increases dose proportionately with peak concentrations in plasma occurring 5 to 8 h postdose (8). Posaconazole is widely distributed into the tissues ($V/F \sim 600$ liters) and has a long terminal elimination half-life ($t_{1/2} \sim 25$ to 31 h). Food enhances posaconazole absorption, with consumption of a nonfat or high-fat meal increasing the exposure (AUC) of the posaconazole oral suspension by 2.6- and 4-fold, respectively, compared to the fasting state (9). In subjects given posaconazole under fasting conditions, bioavailability is enhanced when the drug is administered in divided doses (F. Ezzet, D. Wexler, R. Courtney, M. Laughlin, and V. Batra, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1393, 2002). Based on its excellent in vitro activity (19, 24, 26), preliminary in vivo efficacy and initial clinical safety data (R. Hachem, I. Raad, C. Afif, R. Negroni, J. Graybill, S. Haydley, H. Kantarjian, S. Adams, and G. Mukwawa, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1059, 2000; A. J. Ullmann, O. A. Cornely, A. Burchardt, C. Huber, R. Hachem, D. P. Kontoyiannis, K. Tolpelt, J. Lahey, F. Ezzet, R. Courtney, G. Corcoran, and I. Raad, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-1257, 2003), and predictable pharmacokinetic characteristics (8), posaconazole is expected to provide an effective agent for the treatment of mycoses in immunocompetent and immunodeficient patients.

In addition to being at risk for opportunistic fungal infections, immunodeficient patients are susceptible to various gastrointestinal disorders. For example, AIDS patients frequently experience periods of suppressed gastric acid secretion (14, 28), and critically ill patients are commonly administered acid-suppressive agents for the treatment of stress-related mucosal disease (10). Thus, while receiving therapeutic or prophylactic antifungal treatment, these patients may also require antacid administration to control spontaneous or drug-induced hyperchlorhydria. Many currently marketed antifungal agents, such as ketoconazole and itraconazole, are poorly absorbed under conditions of elevated pH. Ketoconazole and itraconazole are weak bases that are ionized at a low pH, rendering these agents more soluble in water under acidic conditions (5). Conseq-
frequently, the dissolution and absorption of these antifungal agents are substantially reduced when administered concomitantly with gastric acid suppressants (i.e., histamine H2-receptor antagonists) or neutralizing agents (i.e., antacids) or during periods of gastric hypoaemia (4, 15, 17, 18).

Chemically, posaconazole is structurally related to itraconazole and has physicochemical properties similar to those of both itraconazole and ketoconazole. In light of these similarities, it is possible that the pharmacokinetics of posaconazole may also be affected by alterations in gastric pH. Thus, this study was conducted to evaluate the potential for a pH-dependent Pharmacist interaction between posaconazole and an antacid (Mylanta; Johnson & Johnson-Merck Consumer Pharmaceutical Co., Fort Washington, Pa.), under fasting and nonfasting conditions.

MATERIALS AND METHODS

Subjects. Adult male and female volunteers between 18 and 45 years of age and weighing within 15% of their ideal body weight (predicted weight, using actuarial tables) were eligible for enrollment. Female subjects were required to be without childbearing potential and nonlactating to participate in the study. All subjects were determined to be in good health on the basis of medical history, results of physical examinations, routine laboratory tests, and electrocardiogram (ECG) findings. Subjects were excluded from study participation if they had donated blood or had participated in a clinical trial with an investigational drug within 90 days of study initiation. Subjects were also excluded if they smoked more than 10 cigarettes per day or had a history of a clinically significant local or systemic infection. Use of any drugs (other than acetaminophen) within 2 weeks or consumption of alcohol within 48 h before study drug administration was also prohibited.

Study design and treatment regimens. This randomized, open-label, four-period crossover, single-dose study was conducted to evaluate the potential for a pH-dependent pharmacokinetic interaction between posaconazole and an antacid (Maximum Strength Mylanta, an aluminum hydroxide and magnesium hydroxide antacid providing 25.4 mcg of acid-neutralizing capacity per 5 ml) in human volunteers. In the morning following an overnight fast, each subject received one of four regimens according to a computer-generated random code: posaconazole (two 100-mg tablets) following a 10-h fast, posaconazole (two 100-mg tablets) immediately after 20 ml of Mylanta liquid suspension and following a 10-h fast, posaconazole (two 100-mg tablets) immediately after 20 ml of Mylanta liquid suspension and following a standardized high-fat breakfast, or posaconazole (two 100-mg tablets) following a standardized high-fat breakfast.

The high-fat breakfast consisted of two fried eggs, two strips of bacon, two slices of toast, two pats of butter, hash brown potatoes (4 oz), and whole milk (8 oz). This meal consisted of 31.6 g of protein, 53.8 g of fat, and 57.4 g of carbohydrate, for a total of 841 cal.

Subjects who were randomly assigned to receive the standardized high-fat breakfast consumed the meal within a 20-min period; the assigned treatment was subsequently administered within 5 min of completion of the meal. All treatments were administered with 200 ml of room-temperature noncarbonated water. Posaconazole tablets were swallowed whole, not chewed or crushed. Each treatment was separated by a washout period of 7 days, which was measured from the end of the study phase. Volunteers were under medical supervision throughout their confinement to the study site (72 h postdose).

This study was conducted at the Arkansas Research Medical Testing Center, Little Rock. In accordance with the Declaration of Helsinki, written informed consent and approval by an accredited institutional review board (Arkansas Research Medical Testing Center Human Volunteer Research Committee, Little Rock) were obtained prior to initiation of any study-related activities.

Sample collection and posaconazole concentration determination. Blood samples (6 ml) were collected for plasma posaconazole concentration determination into tubes containing heparin predose (0 h) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 h postdose. Determination of serum posaconazole concentrations was performed as previously described (9). Plasma was separated by centrifugation and frozen to at least –20°C until analyzed. Plasma samples were assayed for posaconazole concentrations by a validated high-performance liquid chromatography assay. The calibration curve for this assay was linear over a concentration of 5 to 5,000 ng/ml. The lower limit of quantitation was 5.00 ng/ml. The percent bias and percent coefficient of variation (CV) at the lower limit of quantitation were 1.9 and 11.9%, respectively. Interassay precision (percent CV) and interassay accuracy (percent bias) were in the ranges of 6.0 to 8.1% and 4.4 to 6.1%, respectively.

Posaconazole pharmacokinetic analyses. Pharmacokinetic analyses were conducted using WinNonLin software (Pharsight, Mountain View, Calif.). Plasma posaconazole concentrations were used to determine the pharmacokinetic parameters by model-independent methods (11). Maximum concentration in plasma (Cmax) and time to Cmax (Tmax) and the final quantifiable sample (t0f) were the observed values. The area under the plasma concentration-time curve from time zero to the time of the final quantifiable sample (AUCt0f) was calculated using the trapezoidal method and was extrapolated to infinity (t) according to the equation:

\[ \text{AUC}_{\text{t0f}} = \text{AUC}_t + c_{\text{intercept}} \times t, \]

where Cintercept is the estimated concentration at tif. The terminal-phase half-life (t1/2) was determined as ln(2)/k, with k calculated as the negative of the slope of the log-linear terminal portion of the plasma concentration-time curve by linear regression. Apparent total body clearance (CL/F) was calculated as the ratio of dose to AUCt0f, and the apparent volume of distribution (V/F) was calculated as V/F = dose/(k • AUCt0f).

Posaconazole statistical analyses. The posaconazole pharmacokinetic parameters were statistically analyzed using a crossover analysis of variance (ANOVA) model with effects due to subject, period, and treatment included. Relative bioavailability estimates, based on log-transformed Cmax and AUCt0f values, were expressed as the ratio of the two treatments. The primary comparisons were (i) posaconazole with antacid relative to posaconazole without antacid (under fasting and nonfasting conditions) and (ii) posaconazole under nonfasting conditions (high-fat meal) relative to posaconazole under fasting conditions (in the presence and absence of antacid). Ninety percent confidence intervals (CI) for these estimates of bioavailability and the power to detect a 20% difference between treatment means for an α level of 0.05 (two-tailed) were also computed. The pooled residual error and associated degrees of freedom from the ANOVA were used in the calculations of the CI and power. Preliminary analysis included examination of the pharmacokinetic parameters for extreme values by review of the Studentized ranges of deviation from the expected value derived from the ANOVA to see if any value exceeded 3. The impact of any outliers on the results of the analyses was evaluated.

Safety evaluations. Physical examinations, ECGs, and clinical laboratory tests were conducted at screening and at the conclusion of the study (72 h postdose). Vital signs were monitored prior to and at frequent intervals following treatment administration, especially during the first 24-h period. An additional ECG was performed at the anticipated Tmax (5 h postdose) (8). Subjects were continuously observed and questioned throughout their confinement for the possible occurrence of adverse events. The study investigator assessed adverse events for severity (mild, moderate, severe, or life-threatening) and determined the relationship of the adverse events to the study drug (unrelated, possibly related, probably related, or related).

RESULTS

Subject demographics. Twelve healthy adult males, with a mean age of 34 years (range, 20 to 42 years) and a mean weight of 77.7 kg (range, 59.1 to 93.2 kg), were enrolled in and completed the study. The races of the enrolled subjects were black (n = 8) and white (n = 4). All 12 subjects were included in the pharmacokinetic and safety analyses. No subject was discontinued prematurely from the study.

Posaconazole pharmacokinetics. Mean pharmacokinetic parameters following administration of a single 200-mg dose of posaconazole alone or in combination with antacid, under fasting and nonfasting conditions, are summarized in Table 1. An AUCt0f could not be determined for all subjects because of a greater than 25% extrapolation of the AUCt0f, therefore, the ratios of the AUCt0f values were used as a measure of relative bioavailability because all t0f values were the same at 72 h. Posaconazole was orally bioavailable following all four treatments. Mean concentration in plasma-time profiles demonstrated that concomitant antacid administration had no statistically significant effect on posaconazole Cmax and AUC values (Table 1 and Fig. 1; P > 0.05). Relative oral bioavailability estimates (expressed as the ratio of posaconazole AUCt0f values

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with antacid to those without antacid) were 88% (90% CI, 71 to 110) and 115% (90% CI, 92 to 143) under nonfasting and fasting conditions, respectively (Table 2). Administration of posaconazole alone and in combination with antacid resulted in mean AUC<sub>tf</sub> values of 10,220 and 9,513 ng·h/ml, respectively, under nonfasting conditions and 2,718 and 2,930 ng·h/ml, respectively, under fasting conditions (Table 1). Posaconazole AUC<sub>tf</sub> values exhibited moderate intrasubject variability in all four treatment groups (29 to 45%) (Fig. 2).

In the presence or absence of antacid, mean C<sub>max</sub> values were increased significantly (P = 0.001) under nonfasting conditions (326 and 366 ng/ml, respectively) relative to fasting conditions (94.6 and 92.5 ng/ml, respectively) (Table 1 and Fig. 1). When the drug was administered with a high-fat meal, posaconazole AUC<sub>tf</sub> values were approximately fourfold higher than those in the fasting state (Table 1). Posaconazole AUC<sub>tf</sub> values exhibited moderate intrasubject variability in all four treatment groups (29 to 45%) (Fig. 2).

The median T<sub>max</sub> was 8.7 h and was unaltered among the four treatment groups (range, 6 to 9 h).

The t<sub>1/2</sub> of posaconazole was approximately 19 h and, like T<sub>max</sub>, was unaffected by food or antacid coadministration. CL/F ranged from 323 to 1,072 ml/min and was higher in the fasting state than in the nonfasting state. In addition, the apparent V/F was extensive in all groups (range, 526 to 1,709 liters); however, V/F values were higher in fasting subjects.

**Safety.** One subject reported one adverse event (headache) following administration of posaconazole and antacid under nonfasting conditions. This adverse event was considered mild but possibly related to posaconazole administration. No clinically significant changes in ECG parameters, routine laboratory values, or vital signs were observed.

**DISCUSSION**

The results from this study identify two important findings: (i) posaconazole absorption is not pH dependent, and (ii) a high-fat meal significantly increases posaconazole exposure. The lack of a statistically significant difference in posaconazole pharmacokinetic parameters following coadministration of antacid and posaconazole, under nonfasting or fasting conditions, suggests that posaconazole absorption is not influenced by changes in gastric pH. Although antacid increased the rel-

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**TABLE 1. Mean (percent CV) pharmacokinetic parameters of posaconazole administered alone and in combination with antacid, under nonfasting and fasting conditions (n = 12)**

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Nonfasting</th>
<th></th>
<th>Fasting</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With antacid</td>
<td>Alone</td>
<td>With antacid</td>
<td>Alone</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>326 (47)</td>
<td>366 (28)</td>
<td>94.6 (36)</td>
<td>92.5 (46)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>8.5 (41)</td>
<td>7.6 (42)</td>
<td>8.9 (40)</td>
<td>9.0 (47)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;cf&lt;/sub&gt; (ng·h/ml)</td>
<td>9,513 (45)</td>
<td>10,220 (31)</td>
<td>2,718 (29)</td>
<td>2,718 (41)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;I&lt;/sub&gt; (ng·h/ml)</td>
<td>10,625 (47)</td>
<td>11,068 (31)</td>
<td>2,976 (26)</td>
<td>3,323 (33)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>20.4 (18)</td>
<td>18.3 (14)</td>
<td>18.5 (33)</td>
<td>19.0 (30)</td>
</tr>
<tr>
<td>CL/F (ml/min)</td>
<td>345 (40)</td>
<td>323 (26)</td>
<td>1,072 (18)</td>
<td>1,062 (35)</td>
</tr>
<tr>
<td>V/F (liters)</td>
<td>623 (55)</td>
<td>526 (34)</td>
<td>1,671 (44)</td>
<td>1,709 (37)</td>
</tr>
</tbody>
</table>

**TABLE 2. Relative oral bioavailability estimates and 90% CI of posaconazole when administered with antacid relative to those for posaconazole administered alone**

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Nonfasting</th>
<th></th>
<th>Fasting</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bioavailability estimate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90% CI</td>
<td>P</td>
<td>Bioavailability estimate&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>84</td>
<td>64–109</td>
<td>0.241</td>
<td>107</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;tf&lt;/sub&gt; (ng·h/ml)</td>
<td>88</td>
<td>71–110</td>
<td>0.352</td>
<td>115</td>
</tr>
</tbody>
</table>

<sup>a</sup>Expressed as a ratio of posaconazole with antacid to posaconazole alone.

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**FIG. 1. Mean concentration in plasma-time profile of posaconazole alone and in combination with antacid under nonfasting and fasting conditions.**
ative oral bioavailability by 15% in the fasting state and decreased the relative oral bioavailability by 12% in the nonfasting state, because of intersubject variability in the AUC<sub>tf</sub> values, these small and inconsistent changes in relative oral bioavailability are not considered clinically significant.

Posaconazole is a lipophilic drug with high permeability (＞10<sup>-5</sup> cm/s), low aqueous solubility (<1 µg/ml), and a pK<sub>a</sub> of 3.6 for the piperazine nitrogen and 4.6 for the triazole nitrogen. The observation that antacid does not significantly affect the absorption of posaconazole is noteworthy because some currently marketed antifungal agents are poorly absorbed under conditions of elevated gastric pH (16, 17). Administration of ketoconazole to healthy fasting volunteers in a simulated state of achlorhydria reduced ketoconazole <i>C</i><sub>max</sub> and <i>AUC</i> values by 93 and 92%, respectively, compared with fasting control subjects (17). Similarly, elevated gastric pH decreased itraconazole <i>C</i><sub>max</sub> and <i>AUC</i> values by approximately 50% in two separate studies (<i>P</i> < 0.011) (16, 18). Because impaired absorption may play a significant role in therapeutic failures, a number of studies have explored the effect of oral coadministration of these azole compounds with a palatable acidic beverage, with the objective of improving oral bioavailability. Consumption of a carbonated cola beverage (pH ~ 2.5) reduces gastric pH; however, it only partially restores the exposure of ketoconazole and itraconazole to control levels (7, 16). More importantly, acidifying the gastric compartment with a cola beverage to improve ketoconazole and itraconazole absorption counteracts the potentially therapeutic effect of antacid coadministration. Collectively, these observations emphasize the need for a broad-spectrum antifungal compound with predictable pharmacokinetics that is well absorbed regardless of alterations in gastric pH.

The results of the present study confirm that food substantially influences the extent of posaconazole absorption. Enhancement of posaconazole absorption with food was observed in a recent clinical trial in which the bioavailability of a posaconazole oral suspension was evaluated under nonfasting (high-fat and nonfat meals) and fasting conditions (9). Relative oral bioavailability estimates, based on <i>AUC</i> and <i>C</i><sub>max</sub> values, were 4-fold and 2.6-fold greater following administration of the suspension formulation. In the present study, administration of the tablet formulation of posaconazole with a high-fat meal resulted in <i>AUC</i> concentrations that were fourfold greater and were comparable to those previously observed with the suspension formulation. Taken together, these observations demonstrate that consumption of a meal containing fat calories will increase the relative oral bioavailability of posaconazole by approximately 400% regardless of which formulation is administered (tablet versus suspension).

Food influences the pharmacokinetics of some currently marketed azole antifungal agents. The oral bioavailability of ketoconazole is increased by 34% when administered with a high-fat meal (17). Conversely, a high-fat meal reduces steady-state voriconazole <i>C</i><sub>max</sub> and <i>AUC</i> values by 24 and 34%, respectively (voriconazole [VFEND] prescribing information, Pfizer Inc., New York, N.Y., 2002). In the case of itraconazole,

![FIG. 2. Individual posaconazole AUC<sub>tf</sub> values following administration of posaconazole alone and in combination with antacid under nonfasting (fed) and fasting conditions.](http://aac.asm.org/)

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>With antacid</th>
<th>Without antacid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bioavailability estimate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90% CI</td>
</tr>
<tr>
<td>&lt;i&gt;C&lt;/i&gt;&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>330</td>
<td>256–426</td>
</tr>
<tr>
<td>&lt;i&gt;AUC&lt;/i&gt;&lt;sub&gt;tf&lt;/sub&gt; (ng · h/ml)</td>
<td>308</td>
<td>247–384</td>
</tr>
</tbody>
</table>

<sup>a</sup>Expressed as a ratio of posaconazole under nonfasting conditions to that under fasting conditions.
the effect of food on its relative oral bioavailability varies according to which formulation is administered (2, 3, 31). Itraconazole bioavailability increases nearly twofold when the capsule formulation is administered with food relative to the fasting state (31). In contrast, food decreases the bioavailability of the itraconazole solution formulation by approximately 30% (3). In light of the variability observed with itraconazole bioavailability between formulations, it is noteworthy that posaconazole bioavailability increases consistently with food regardless of the formulation administered (9).

In conclusion, antacid has a small, clinically insignificant effect on posaconazole oral bioavailability in both the fasting and the nonfasting state, suggesting that posaconazole absorption is not pH dependent. In the presence of a meal containing fat calories, the bioavailability of posaconazole increases fourfold. In addition, posaconazole administered as a single 200-mg dose alone or in combination with antacid, under nonfasting or fasting conditions, is safe and well tolerated. These observations are of particular relevance to critically ill patients who may require gastric acid suppression for the prevention or management of stress-related mucosal disease (10). Furthermore, AIDS patients with invasive fungal infections, in whom gastric acidity is often compromised (14, 28), could also potentially benefit from an antifungal agent that is unaffected by elevated gastric pH.

REFERENCES


