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Posaconazole Tablet Pharmacokinetics: Lack of Effect of Concomitant Medications Altering Gastric pH and Gastric Motility in Healthy Subjects.

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Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; MSD, Oss, Netherlands; Merck & Co., Inc., Whitehouse Station, New Jersey, USA.

Posaconazole oral suspension is an extended-spectrum triazole that should be taken with food to maximize absorption. A new posaconazole tablet formulation has demonstrated improved bioavailability over the oral suspension in healthy adults in a fasting state. This study evaluated the effects of concomitant medications altering gastric pH (antacid, ranitidine, and esomeprazole) and gastric motility (metoclopramide) on the pharmacokinetics of posaconazole tablets. This was a prospective open-label 5-way crossover study in 20 healthy volunteers. In each treatment period, a single 400-mg dose (4 100-mg tablets) of posaconazole was administered alone or with 20 mL antacid (2 g of aluminum hydroxide and 2 g of magnesium hydroxide), ranitidine (150 mg), esomeprazole (40 mg), or metoclopramide (15 mg). There was a ≥10-day washout between treatment periods. Posaconazole exposure, time to maximum concentration of drug in serum ($T_{\text{max}}$), and apparent terminal half-life ($t_{\text{1/2}}$) were similar when posaconazole was administered alone or with medications affecting gastric pH and gastric motility. Geometric mean ratios (90% confidence intervals [CIs]) of the area under the concentration-time curve from time zero to infinity ($\text{AUC}_{0-\text{inf}}$) (posaconazole with medications affecting gastric pH and gastric motility versus posaconazole alone) were 1.03 (0.88–1.20) with antacid, 0.97 (0.84–1.12) with ranitidine, 1.01 (0.87–1.17) with esomeprazole, and 0.93 (0.79–1.09) with metoclopramide. Geometric mean ratios (90% CIs) of the maximum concentration of drug in serum ($C_{\text{max}}$) were 1.06 (0.90–1.26) with antacid, 1.04 (0.88–1.23) with ranitidine, 1.05 (0.89–1.24) with esomeprazole, and 0.86 (0.73–1.02) with metoclopramide. In summary, in healthy volunteers, the pharmacokinetics of a single 400-mg dose of posaconazole tablets was not altered to a clinically meaningful extent when posaconazole was administered alone or with medications affecting gastric pH or gastric motility.

Posaconazole oral suspension (Noxafil; Merck & Co., Inc., Whitehouse Station, NJ, USA) is a marketed extended-spectrum triazole with demonstrated efficacy as prophylaxis and treatment for patients with invasive fungal infection (IFI) (1–5). Posaconazole is approved in more than 80 countries worldwide. In the United States and Europe, posaconazole is approved for the prophylaxis of IFI in immunocompromised patients and for the treatment of those with oropharyngeal candidiasis (6, 7). Additionally, posaconazole is approved in Europe as a treatment for patients with refractory IFI (7). In a large, multicenter, phase III, randomized clinical trial in patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome, treatment with 200 mg of posaconazole oral suspension 3 times daily (compared with fluconazole or itraconazole) resulted in fewer proven or probable IFIs (2% versus 8%; $P < 0.001$), a statistically significantly lower incidence of invasive aspergillosis (1% versus 7%), and longer survival ($P = 0.04$) (1). In a large, randomized, double-blind, phase III trial in patients with graft-versus-host disease, 200 mg of posaconazole oral suspension 3 times daily was similar to fluconazole for prophylaxis against IFI and was superior in preventing invasive aspergillosis (2.3% versus 7%; $P = 0.006$) and reducing the rate of death related to fungal infections (1% versus 4%; $P = 0.01$) (4). In an externally controlled study in patients with invasive aspergillosis refractory to or intolerant of amphotericin B and/or itraconazole, 200 mg of posaconazole oral suspension 4 times daily demonstrated activity for the treatment of invasive aspergillosis with an overall success rate of 42% for posaconazole recipients compared with a rate of 26% for control subjects ($P = 0.006$) (5).

The pharmacokinetics (PK) of posaconazole oral suspension has been extensively studied in both healthy volunteers and patients at risk for IFI (8–15). The bioavailability of posaconazole oral suspension is significantly enhanced when coadministered with food, particularly a high-fat meal (12, 16). However, those at high risk for IFI, such as neutropenic patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome and recipients of allogeneic hematopoietic stem cell transplants, may be unable to eat because of mucositis, nausea, or neutropenic enterocolitis (14, 17, 18). The posaconazole label recommends that posaconazole oral suspension be administered with food or a nutritional supplement to ensure that adequate plasma concentrations are attained (6, 7). In patients unable to eat, the absorption of posaconazole oral suspension may be enhanced by dividing the posaconazole doses (200 mg 4 times daily) or by administering the drug with a liquid nutritional supplement or acidic beverage such as ginger ale (10, 12).

The PK of posaconazole oral suspension has been studied in...
combination with esomeprazole, which increases gastric pH, and metoclopramide, which increases gastric motility (12). The administration of 400 mg of posaconazole oral suspension to healthy volunteers under conditions of increased gastric pH (coadministered esomeprazole) decreased posaconazole exposures (mean area under the concentration-time curve [AUC]) by 32% and 21% under fasting conditions and in the presence of an acidic carbonated beverage, respectively. Furthermore, administration of 400 mg of posaconazole oral suspension under conditions of increased gastric motility (coadministered metoclopramide) decreased posaconazole exposure (mean AUC) by 19% (geometric mean ratio [GMR], 0.81; 90% confidence interval [CI] = 0.72 to 0.91) in the presence of a nutritional supplement (12).

A new oral tablet formulation of posaconazole has been developed. The posaconazole tablet formulation consists of active drug mixed with a pH-sensitive polymer (hypromellose acetate succinate [HPMCAS]), which limits POS release from the tablet when mixed with a pH-sensitive polymer (hypromellose acetate succinate [HPMCAS]), which limits POS release from the tablet when exposed to a low gastric pH and releases POS at the elevated pH of the intestine. Furthermore, it is believed that the presence of the polymer in the intestinal fluid inhibits the recrystallization of POS, thus ensuring that a greater fraction of the dose is available for absorption. This results in substantially improved exposure (~3-fold) compared with that for the oral suspension in healthy adults in the fasting state (19). This attribute of posaconazole tablets may be beneficial in patients with poor food intake or a limited ability to take the medication with a high-fat meal.

Because the tablet design exploits the pH environment of the small intestine to maximize absorption, we wanted to evaluate the PK and safety of posaconazole tablets in the presence of agents that alter gastric pH and gastric motility. In the present study, we investigated the effects of antacid, ranitidine, esomeprazole, and metoclopramide on posaconazole tablet PK and safety. Antacid, ranitidine (an H2 receptor functional antagonist), and esomeprazole (a proton pump inhibitor) were chosen because they increase gastric pH in different ways. Metoclopramide, which stimulates gastric motility, was chosen because it is commonly prescribed to treat chemotherapy-induced nausea.

Subjects who tested positive for the human immunodeficiency virus, hepatitis B virus surface antigen, or hepatitis C virus were also excluded.

**Treatment.** Subjects received all 5 treatments in a randomized, crossover manner with a ≥10-day washout period between each posaconazole dose. The study drugs were administered in the fasting state (~10 h after an overnight fast), with the first meal approximately 4 h postdose on day 1. In each period, subjects received one of the following:

- A single 400-mg dose (4 100-mg tablets) of posaconazole tablets administered alone on day 1.
- Posaconazole (400 mg) plus 20 ml of antacid (Mylanta ultimate strength liquid [2 g of aluminum hydroxide/2 g of magnesium hydroxide]; McNeil Consumer Pharmaceuticals, Fort Washington, PA) on day 1; posaconazole tablets were administered immediately after antacid.
- Posaconazole (400 mg) plus ranitidine (150 mg twice daily) on day 1; posaconazole tablets were administered 1 h after the first dose of ranitidine.
- Posaconazole (400 mg) on day 1 plus esomeprazole (40 mg once in the morning for 5 days [days −4 to 1]); posaconazole tablets were administered at the same time as esomeprazole.
- Posaconazole (400 mg) on day 1 plus metoclopramide (15 mg 4 times daily for 2 days [days −1 and 1]); posaconazole tablets were administered at the same time as metoclopramide.

**Pharmacokinetic analysis.** Blood samples (4 ml) for PK evaluation of posaconazole in plasma were collected in each treatment period predose (0 h) and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, and 168 h postdose. The samples were drawn into prechilled K2 EDTA-containing tubes and were centrifuged within 30 min of collection at 1,500 × g for 15 min in a refrigerated centrifuge (4°C). The plasma was stored at −20°C until analyzed. The samples were transferred to the analytical site on dry ice. The plasma samples were assayed for posaconazole using a previously described validated liquid chromatography with tandem mass spectrometric detection method (20) with a lower limit of quantitation of 5 ng/ml and a calibration range of 5 to 5,000 ng/ml.

**TABLE 1 Subject demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data for all subjects (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median [range]) (yr)</td>
<td>38 (24–33)</td>
</tr>
<tr>
<td>Sex (no. [%])</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Race (no. [%])</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7 (33)</td>
</tr>
<tr>
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<td>13 (62)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Ethnicity, not Hispanic/Latino</td>
<td></td>
</tr>
<tr>
<td>Weight (median [range]) (kg)</td>
<td>78.2 (52.5–105.1)</td>
</tr>
<tr>
<td>Height (median [range]) (cm)</td>
<td>175 (158–186.5)</td>
</tr>
<tr>
<td>Body mass index (median [range]) (kg/m²)</td>
<td>25.9 (21.0–31.7)</td>
</tr>
</tbody>
</table>

**MATERIALS AND METHODS**

**Subjects.** This was a randomized prospective open-label 5-way crossover study in healthy volunteers. It was conducted in accordance with the principles of good clinical practice, and written informed consent was obtained from each subject before any study-related procedures were performed. The protocol was reviewed and approved by an independent ethics committee (Thomas Jefferson University, PA).

**Inclusion and exclusion criteria.** Healthy male and female subjects of any race, who were 18 to 55 years of age (inclusive) and had a body mass index between 18 and 32 kg/m2 (inclusive), were eligible to be enrolled. Subjects who smoked >10 cigarettes per day (or used an equivalent amount of any tobacco product) were excluded.

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</table>
TABLE 2 Arithmetic means (CV) of the pharmacokinetic parameters of posaconazole after single-dose administration of posaconazole tablets (400 mg) alone or with concomitant medications to healthy volunteers.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>C_{max} (ng/ml)</th>
<th>AUC_{0–inf} (h·ng/ml)</th>
<th>AUC_{0–last} (h·ng/ml)</th>
<th>T_{max} (h)</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POS alone</td>
<td>1,090 (43)</td>
<td>42,406 (49)</td>
<td>40,967 (47)</td>
<td>4 (2–8)</td>
<td>27.3 (37)</td>
</tr>
<tr>
<td>POS + antacid</td>
<td>1,112 (36)</td>
<td>42,468 (39)</td>
<td>41,247 (39)</td>
<td>4.8 (3–12)</td>
<td>27.7 (29)</td>
</tr>
<tr>
<td>POS + ranitidine</td>
<td>1,094 (37)</td>
<td>39,287 (37)</td>
<td>38,046 (35)</td>
<td>4 (3–5)</td>
<td>26.9 (35)</td>
</tr>
<tr>
<td>POS + esomeprazole</td>
<td>1,104 (35)</td>
<td>41,574 (43)</td>
<td>40,083 (40)</td>
<td>4.5 (3–24)</td>
<td>28.0 (30)</td>
</tr>
<tr>
<td>POS + metoclopramide</td>
<td>935 (44)</td>
<td>38,513 (45)</td>
<td>36,975 (40)</td>
<td>4 (2–6)</td>
<td>29.0 (38)</td>
</tr>
</tbody>
</table>

\(^{a}\) AUC_{0–inf} area under the concentration–time curve from time zero to infinity; AUC_{0–last} area under the concentration–time curve from time zero to time of the last quantifiable sample; C_{max}, maximum observed concentration of drug in serum; CV, coefficient of variation; POS, posaconazole; T_{max}, time to C_{max}; t_{1/2}, apparent terminal half-life.

\(^{b}\) Median (minimum to maximum).

TABLE 3 GMRs (90% CI) of AUC_{0–inf}, AUC_{0–last}, and C_{max} for posaconazole plus treatment compared with those for posaconazole tablet alone.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>C_{max}</th>
<th>AUC_{0–inf}</th>
<th>AUC_{0–last}</th>
</tr>
</thead>
<tbody>
<tr>
<td>POS + antacid</td>
<td>1.06 (0.90–1.26)</td>
<td>1.03 (0.88–1.20)</td>
<td>1.04 (0.90–1.20)</td>
</tr>
<tr>
<td>POS + ranitidine</td>
<td>1.04 (0.88–1.23)</td>
<td>0.97 (0.84–1.12)</td>
<td>0.97 (0.84–1.12)</td>
</tr>
<tr>
<td>POS + esomeprazole</td>
<td>1.05 (0.89–1.24)</td>
<td>1.01 (0.87–1.17)</td>
<td>1.02 (0.88–1.17)</td>
</tr>
<tr>
<td>POS + metoclopramide</td>
<td>0.86 (0.73–1.02)</td>
<td>0.93 (0.79–1.09)</td>
<td>0.93 (0.80–1.07)</td>
</tr>
</tbody>
</table>

\(^{a}\) AUC_{0–inf} area under the concentration–time curve from time zero to infinity; AUC_{0–last} area under the concentration–time curve from time zero to time of the last quantifiable sample; CI, confidence interval; C_{max}, maximum observed concentration of drug in serum; GMR, geometric mean ratio; POS, posaconazole.

effects model, extracting the effects due to treatment, period, and sequence as fixed effects and effects due to subjects as random effect; a log transformation was applied and back transformed. Geometric mean ratios (GMRs) of AUC_{0–last}, AUC_{0–inf}, and C_{max} (posaconazole plus each concomitant treatment versus posaconazole alone) and 90% confidence intervals (CIs) were provided from the linear mixed-effects model. If the 90% CI fell within the range of 0.5 to 2.0, it was assumed there was no clinically meaningful effect of gastric pH or gastric motility on posaconazole PK.

Safety analysis. Safety assessments included reporting of adverse events (AEs), vital signs, physical examination, ECG, hematology, and blood chemistry through day 8 of the last treatment period. The AEs were tabulated by body system or organ class and severity and were summarized by treatment.

RESULTS

Subject demographics. Twenty-one subjects were enrolled in the study (Table 1). Eighty-six percent of them were male, and 62% were black or African American; the mean age was 38 years. Twenty subjects completed the study; 1 subject withdrew consent and discontinued after the first treatment period. The subject withdrew consent on day 1 of period 1 and received only a single dose of antacid and a single oral dose of 400 mg of posaconazole.

Pharmacokinetics. Posaconazole AUC_{0–last}, AUC_{0–inf}, C_{max}, T_{max}, and t_{1/2} values were similar whether posaconazole was administered alone or with medications affecting gastric pH and gastric motility (Table 2). The mean (percent coefficient of variation [%CV]) C_{max} values for posaconazole were 1,090 ng/ml (43) when administered alone compared with 1,112 ng/ml (36), 1,094 ng/ml (37), 1,104 ng/ml (35), and 935 ng/ml (44) when administered with antacid, ranitidine, esomeprazole, and metoclopramide, respectively. Similarly, mean (CV) AUC_{0–inf} values for posaconazole were 42,406 h·ng/ml (49) when administered alone compared with 42,468 h·ng/ml (39), 39,287 h·ng/ml (37), 41,574 h·ng/ml (43), and 38,513 h·ng/ml (43) when administered with antacid, ranitidine, esomeprazole, and metoclopramide, respectively. Results were similar for AUC_{0–last} (Table 2). Median T_{max} and t_{1/2} also appeared to be unaffected by concomitant medication; T_{max} ranged from 4 to 4.8 h, and t_{1/2} ranged from 27 to 29 h.

The mean plasma concentration–time profiles of posaconazole tablets administered alone and with antacid, ranitidine, esomeprazole, and metoclopramide are similar (Fig. 1). AUC_{0–last}, AUC_{0–inf}, and C_{max} GMRs (90% CIs) of posaconazole tablets plus treatment versus posaconazole tablets alone are summarized in Table 3, and AUC_{0–last} and C_{max} GMRs (90% CIs) are presented graphically in Fig. 2. AUC_{0–inf} GMRs of posaconazole plus treatment compared with that for posaconazole alone were 1.03 for antacid, 0.97 for ranitidine, 1.01 for esomeprazole, and 0.93 for metoclopramide. Similarly, C_{max} GMRs of posaconazole plus treatment compared with that for posaconazole alone were 1.06 for antacid, 1.04 for ranitidine, 1.05 for esomeprazole, and 0.86 for metoclopramide. The 90% CIs of AUC_{0–last}, AUC_{0–inf}, and C_{max} for each comparison to posaconazole alone were fully contained within the prespecified bounds of 0.5 to 2.0; there was, therefore, no clinically meaningful effect of gastric pH or gastric motility on the PK of posaconazole tablets.

FIG 1 Arithmetic mean plasma concentration–time profiles after single-dose administration of posaconazole (POS) tablets (400 mg) alone or with concomitant medications to healthy volunteers (inset, semilog scale). n = 20 (except for posaconazole + antacid, where n = 21).
Safety. Overall, 19 of 21 (90%) subjects reported at least 1 treatment-emergent AE; all AEs were mild to moderate in severity. No deaths, serious AEs, or significant AEs were reported, and no subjects discontinued treatment because of AEs. The most frequent treatment-emergent AEs were somnolence (8 subjects [38%]), diarrhea (7 subjects [33%]), contusion (6 subjects [29%]), and flatulence (5 subjects [24%]). Fourteen (67%) subjects reported 1 AE considered to be treatment related; the most frequent treatment-related AEs were somnolence (7 subjects [33%]), diarrhea (5 subjects [24%]), and flatulence (3 subjects [14%]). The remaining treatment-related AEs were reported by only 1 subject each. Dosing was temporarily halted in 2 subjects because of AEs (elevated creatine phosphokinase [CPK] and oromandibular dystonia); these AEs were transient, and the subjects remained in the study through completion. The elevated CPK was not considered treatment related, whereas oromandibular dystonia was considered to be probably treatment related with the coadministered drug metoclopramide. Apart from the elevated CPK in 1 subject, no laboratory AEs were reported. No clinically significant changes were observed in vital signs or ECG findings in any treatment group.

DISCUSSION
This randomized, open-label, single-center, 5-way crossover, single-dose study evaluated the effects of concomitant medications that alter gastric pH and gastric motility on the PK of posaconazole tablets in healthy volunteers. The PK of a single 400-mg dose of posaconazole tablets was found to be similar when the drug was administered alone and when it was administered with antacid, ranitidine, esomeprazole, or metoclopramide. The AUC_{0–inf} GMRs of posaconazole plus treatment compared with that of posaconazole alone ranged from 0.93 to 1.03, whereas the associated C_{max} GMRs ranged from 0.86 to 1.06. All 90% CIs of AUC_{0–last}, AUC_{0–inf}, and C_{max} for each comparison to posaconazole alone were fully contained within the prespecified limits of 0.5 to 2.0, therefore confirming that there was no clinically meaningful effect of gastric pH or gastric motility on the PK of the posaconazole tablets. Hence, it appears that posaconazole tablets may be coadministered with gastric agents without decreasing posaconazole exposure. The largest point estimate difference was seen in the metoclopramide coadministration with 93% systemic exposure (AUC) compared to that for posaconazole alone. However, the magnitude of the difference is considered not clinically relevant, and as the 90% CIs spanned 79% to 109% (AUC_{0–inf}), the difference was not statistically significant. Although the increased exposure of the tablet formulation compared with that of the oral suspension, especially under fasted conditions, may benefit patients at risk for low absorption of posaconazole such as those unable to take the currently marketed oral suspension with food (19), it is possible that posaconazole tablets may also be beneficial in patients taking concomitant medications affecting gastric pH or gastric motility.

In a previous study (12), 400 mg of posaconazole oral suspen-
sion was administered in healthy volunteers under conditions of increased gastric pH (coadministered esomeprazole) or increased gastric motility (coadministered metoclopramide). In contrast to the present study, posaconazole exposure was decreased with esomeprazole administered under fasting conditions and in the presence of an acidic carbonated beverage and with metoclopramide administered in the presence of a nutritional supplement (12). The discrepancies in the results between the 2 posaconazole formulations are consistent with what is understood about how the formulations are absorbed. The oral suspension is expected to dissolve in the stomach at low pH; therefore, a lesser amount of drug is likely to be dissolved if the gastric pH is elevated or if the gastric residence time is short. In contrast, with the tablet formulation, the drug is primarily released from the polymer in the small intestine; hence, the drug release is relatively independent of the gastric pH or residence time.

Posaconazole plasma levels are important for maintaining efficacy during both prophylaxis and treatment. Although a threshold posaconazole plasma level allowing for breakthrough IFI has not yet been defined, one study has shown that the median average plasma concentration of posaconazole was lower in 5 allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease who developed breakthrough IFIs while on posaconazole prophylaxis than in 241 patients who did not develop breakthrough IFIs (11). Furthermore, a positive correlation between exposure and response has been reported in a nonrandomized trial of posaconazole salvage treatment for invasive aspergillosis (5). Maintenance of posaconazole plasma concentrations may be critical in patients at risk for IFI who must take concomitant medications that affect gastric pH or gastric motility. In addition to the PK findings in the present study, the 400-mg dose of posaconazole tablets was well tolerated when administered alone or in combination with antacid, ranitidine, esomeprazole, or metoclopramide. This finding is of clinical relevance because these drugs may be prescribed concomitantly with posaconazole.

In conclusion, the PK of a single 400-mg dose of posaconazole tablets is not altered to a clinically meaningful extent when the drug is administered alone or with medications affecting gastric pH or gastric motility in healthy volunteers. These results suggest that posaconazole tablets may be coadministered with gastric agents (antacid, ranitidine, esomeprazole, or metoclopramide) without a clinically important reduction in bioavailability.

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REFERENCES


