Effect of a Nutritional Supplement on Posaconazole Pharmacokinetics following Oral Administration to Healthy Volunteers

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We conducted a randomized, crossover study in healthy adults to examine the effects of a nutritional supplement (Boost Plus) on posaconazole pharmacokinetics. In this study, coadministration of posaconazole with Boost Plus increased the maximum concentration of posaconazole in serum and area under the concentration-time curve from 0 to 72 h values 3.4- and 2.6-fold, respectively, compared to those for the fasted state.

Posaconazole is an orally bioavailable triazole antifungal agent currently in development for the treatment and prophylaxis of invasive fungal infections. It has potent in vitro activity against a wide array of pathogenic fungi (5–7, 10, 11), and clinical trial results have shown it to be well tolerated and effective against several mycoses, including aspergillosis, zygomycosis, coccidioidomycosis, and fusariosis (1).

Steady-state concentrations are attained by 7 to 10 days of multiple-dose administration. Posaconazole does not appear to have any major circulating phase 1 (cytochrome P450) metabolites; most (77%) of an administered dose is excreted as a parent compound in the feces (9). Of the circulating metabolites, most are glucuronide conjugates of posaconazole (9). Although posaconazole is an inhibitor of liver cytochrome P450 3A4 enzyme activity, it has no effect on the activity of other P450 enzymes (12).

Previous studies have demonstrated that food, particularly meals high in fat content, significantly increases posaconazole bioavailability (2, 3). Systemic exposure to posaconazole increases 4- and 2.6-fold when it is consumed with a high-fat and nonfat meal, respectively, relative to that observed in fasted subjects (2). Therefore, posaconazole should be administered with food whenever possible to ensure optimal absorption (2). However, persons at risk for invasive fungal infection are usually critically ill, and many have difficulty eating solid foods. These patients are commonly given liquid nutritional supplements through an enteral feeding tube.

We have therefore conducted an open-label, single-center, randomized study to evaluate the effect of a liquid nutritional supplement (Boost Plus) on the pharmacokinetics of posaconazole. Healthy male and female subjects between the ages of 18 and 55 years, with a body mass index between 19 and 27 kg/m2, were eligible for enrollment. Subjects were excluded if they used prescription or over-the-counter medications (other than acetaminophen) 2 weeks prior to study initiation. Subjects were not permitted to eat again until 4 h postdose following assessment of vital signs and blood sample collection. Each 240-ml serving of Boost Plus contained 360 cal, with a caloric distribution of 16% protein, 34% fat, and 50% carbohydrate. Blood samples (4 ml) were collected predose and up to 72 h postdose on days 1 and 15. The collection of blood samples and assay of plasma posaconazole concentrations were performed using a validated liquid chromatography with tandem mass spectrometric assay with a lower limit of quantitation of 1.00 ng/ml and a linear range of 1.0 to 4,000 ng/ml.

A noncompartmental pharmacokinetic method was used for the analysis (8). The maximum concentration of drug in serum (Cmax) and time to Cmax (Tmax) were observed values. The area under the concentration-time curve from 0 to 72 h (AUC0–72), terminal phase half-life (t1/2), apparent total body clearance, and apparent volume of distribution were calculated using Kinetica 2.5.3. Standard Edition (InnaPhase Corporation, Philadelphia, PA). Safety was assessed on the basis of adverse events, physical examinations, vital signs, clinical assessments of laboratory data, and electrocardiograms.

Summary statistics were prepared, and log-transformed Cmax and AUC values were analyzed using a crossover analysis of variance model. Two-sided 90% confidence interval estimates of the mean ratios of AUC and Cmax were calculated. Twenty-four subjects (12 men and 12 women) were enrolled in the study and received at least 1 dose of posaconazole. Subjects were between the ages of 24 and 53 years (mean age, 39.4 years), and the overall mean body mass index was 26.2 kg/m2. Of the 24 subjects, 16 were Hispanic, 5 were Caucasian, 2 were black, and one was “other.” Twenty-three subjects completed the study and were included in the pharmacokinetic analysis. One subject discontinued the study due to personal reasons. Data from all 24 subjects were used to evaluate safety and tolerability.

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Coadministration of posaconazole and Boost Plus increased drug exposure compared to the administration of posaconazole alone in the fasted state (Fig. 1). Mean C_max and AUC_0–72 values were higher in the presence of Boost Plus than in fasted subjects, resulting in increased relative oral bioavailability (Tables 1 and 2). Median T_max and mean t_{1/2} values were similar in fasted subjects and those receiving Boost Plus (Table 1).

No adverse events were reported following single-dose administration of posaconazole oral suspension with or without Boost Plus despite a significant increase (2.6-fold) in exposure to posaconazole that occurred as a result of Boost Plus coadministration. Vital signs were within normal ranges, and there were no clinically significant changes in routine laboratory test results or electrocardiographic recordings. Mild increases in liver function tests, mostly a single isolated enzyme value, were observed in four subjects, but these were not considered clinically significant, and all resolved spontaneously.

These data demonstrate that coadministration of a liquid nutritional supplement (containing 14 g fat) increases posaconazole bioavailability to an extent similar to that observed with a nonfat meal (2). Concomitant administration of Boost Plus resulted in a statistically significant and marked increase in the bioavailability of the posaconazole suspension relative to T_max in the fasting state. The similarity in T_max and t_{1/2} values observed in the presence and absence of Boost Plus suggests that coadministration of a liquid nutritional supplement increased the extent of posaconazole absorption.

Previous studies have demonstrated that administering posaconazole with food, regardless of fat content, causes an increase in drug exposure (increase of 164% after a nonfat meal); the inclusion of fat in a meal increases posaconazole exposure only by an additional 48% (2, 3). Collectively, these observations indicate that food increases posaconazole bioavailability independent of the type of food (solid versus liquid) or fat content (nonfat versus high fat). Therefore, posaconazole should be administered with food or a nutritional supplement when possible.

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### TABLE 1. Pharmacokinetic parameters for posaconazole following administration of a single 400-mg oral dose given alone while fasted or coadministered with a nutritional supplement (Boost Plus) in 23 healthy volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Posaconazole alone (fasted)</th>
<th>Posaconazole with Boost Plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max (ng/ml)</td>
<td>121 (75)</td>
<td>355 (43)</td>
</tr>
<tr>
<td>T_max (h)</td>
<td>4.0 (2.0–12.0)</td>
<td>5.0 (4.0–8.0)</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>27.3 (26)</td>
<td>26.9 (19)</td>
</tr>
<tr>
<td>AUC_0–72 (ng·h/ml)</td>
<td>5,258 (48)</td>
<td>11,295 (40)</td>
</tr>
<tr>
<td>AUC_{0–72} (ng·h/ml)</td>
<td>3,552 (53)</td>
<td>9,076 (42)</td>
</tr>
<tr>
<td>CL/F (liters/h)</td>
<td>91.2 (40)</td>
<td>42.6 (56)</td>
</tr>
<tr>
<td>V/F (liters)</td>
<td>3,674 (51)</td>
<td>1,573 (51)</td>
</tr>
</tbody>
</table>

* Intersubject variability was 75% in fasted subjects and 43% in subjects receiving Boost Plus.
* Median (range).
* Intersubject variability was 53% in fasted subjects and 42% in subjects receiving Boost Plus.
* n = 10. Area under the plasma concentration-time curve to infinity (AUC_0) could not be determined for 13 of 23 subjects because the extrapolated area under the curve (i.e., AUC from 72 h to infinity) was >25% of the corresponding AUC_{0–72} value.
* CL, clearance; V, volume of distribution; CV, coefficient of variation.

### REFERENCES

