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Superior Serum Concentrations with Posaconazole Delayed-Release Tablets Compared to Suspension Formulation in Hematological Malignancies

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Posaconazole (PCZ), approved for prophylaxis against invasive fungal disease in high-risk patients, is commercially available orally as a suspension formulation (PCZ-susp) and as a delayed-release tablet (PCZ-tab). We evaluated the serum steady-state concentrations (C_{ss}) of PCZ stratified by the administered formulation for antifungal prophylaxis in patients with myeloid malignancies ($n = 150$). The primary outcome was the attainment rate of the target C_{ss} of ≥700 ng/ml. Secondary outcomes included toxicity assessment (hepatotoxicity and corrected QT [QTc] interval prolongation) and breakthrough fungal infections. Patients who received the PCZ-susp ($n = 118$) or PCZ-tab ($n = 32$) and had PCZ C_{ss} assessment after at least 7 days of therapy were eligible. The median C_{ss} in the PCZ-susp group was 390 ng/ml (range, 51 to 1,870 ng/ml; mean, 436 ng/ml) compared to 1,740 ng/ml (range, 662 to 3,350 ng/ml; mean, 1,781 ng/ml) in the PCZ-tab group ($P < 0.0001$). The percentages of patients achieving the target goal of ≥700 ng/ml were 17% versus 97%, respectively ($P < 0.0001$). Hepatotoxicity (grade 2 or higher) occurred in 1 patient in each group. QTc interval measurements were available for 32 patients in the PCZ-susp group and for 12 patients in the PCZ-tab group, and prolonged intervals of grade 2 or higher were noted in 9% ($n = 3$) and 17% ($n = 2$), respectively ($P = 0.6$). Breakthrough fungal infections in the PCZ-susp and PCZ-tab groups were 7% ($n = 8$) and 3% ($n = 1$), respectively ($P = 0.68$). We conclude that the use of PCZ-tab was associated with higher C_{ss} and with the probability of achieving therapeutic goals without worsening of adverse effects.

Posaconazole (PCZ) is a triazole antifungal agent that is approved for invasive fungal disease prophylaxis in high-risk patients. Oral formulations of PCZ are commercially available as a suspension (PCZ-susp) and as delayed-release tablets (PCZ-tab) (1). Several studies have shown that the gastrointestinal absorption and bioavailability of PCZ-susp are unpredictable and dependent on various factors, including food intake and concomitant acid suppressants (2–7). Due to its superior oral bioavailability, the PCZ-tab can be administered without regard to food intake and seems less likely to be affected by concomitant acid-suppressing medications (8–11).

PCZ concentrations follow dose-dependent pharmacokinetics at steady state with saturation of absorption of the PCZ-susp occurring at 800 mg/day (12). The current guidelines recommend as a goal steady-state concentrations (C_{ss}) of ≥700 ng/ml in the prophylaxis setting (13). Comparative studies evaluating the PCZ-susp and the newer PCZ-tab are not available. Herein, we report a retrospective analysis comparing the serum concentrations of the two formulations.

MATERIALS AND METHODS

Patient population. For this study, 152 consecutive patients with acute myelogenous leukemia (AML) or high-grade myelodysplastic syndrome (MDS) who were admitted to the inpatient hematologic malignancy service at West Virginia University Hospital between February 2008 and December 2014 were considered. Adult patients with AML or high-risk MDS undergoing systemic therapy and expected to have prolonged neutropenia (defined as an expected nadir absolute neutrophil count [ANC] of <500/μl and duration of ≥7 to 10 days) and receiving PCZ prophylaxis were included. Patients received PCZ-susp (600 to 800 mg/day) between February 2008 and December 2013 and PCZ-tab (300 mg twice daily on day 1 and then 300 mg once daily) between January 2014 and December 2014. Serum PCZ concentrations were routinely obtained at our institution after at least 7 days of therapy to allow the drug to reach the C_{ss}. The posaconazole doses were administered and witnessed in the inpatient setting. Patients taking concomitant medications (other than agents used for stress ulcer prophylaxis) associated with known significant drug interactions with PCZ were excluded ($n = 2$; drugs were phenytoin and carbamazepine), and thus 150 patients were eligible for this analysis (1). The study was approved by the Institutional Review Board at West Virginia University.

Study definitions and data collection. The primary study outcome was evaluation of the attainment rate of the target PCZ C_{ss} of 700 ng/ml in both groups (13). Secondary endpoints included evaluation of toxicities (hepatotoxicity and QTc prolongation) and breakthrough fungal infections in each group. Of note, the QTc prolongation was not routinely assessed in our patients and was only reported in patients receiving eval-

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uation. The potential impacts of age, obesity, nutritional supplementation, diarrhea, vomiting, and mucositis and the concomitant use of acid-suppressing medications (proton pump inhibitors [PPI] and histamine antagonists [H2A]) on the PCZ C_{ss} were also evaluated.

Food intake and nutritional supplementation were evaluated by a dietitian, who stratified patients into three categories. Category 1 included patients who consumed >75% of meals or >2 nutritional supplements/day, category 2 included patients who consumed 50 to 75% of meals or 1 to 2 nutritional supplements/day, and category 3 included patients who consumed <50% of meals or had no nutritional supplements/day.

Statistical analysis. Descriptive statistics were used to summarize the baseline patient characteristics. Categorical data were described using contingency tables. Continuous variables were summarized using means with standard deviations or medians with ranges. Fisher's exact test was used to assess the independence between two categorical variables, and the Wilcoxon rank sum test was used to assess differences between the 2 groups for continuous variables. Linear regression models were used to assess the PCZ concentrations for the potential impacts of age, dietary status, diarrhea, vomiting, mucositis, and concomitant stress ulcer prophylaxis use. In the multivariate analysis, a multivariable linear model was used to assess the PCZ concentrations with an interaction term of acid suppression and treatment group. Statistical inferences were based on two-sided tests at a significance level of $P < 0.05$. Statistical analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC) and S-PLUS version 7.0 (Insightful Corp., Seattle, WA) software.

Serum posaconazole analysis. A single serum sample was collected from patients receiving PCZ prophylaxis after a minimum of 7 days of therapy to determine the C_{ss}. All serum samples were collected approximately 4 h after the morning dose. Single serum samples were deemed suitable for this study, given the long half-life and minimal daily fluctuation of the drug (2, 14). Serum concentrations of PCZ were determined using a validated high-performance liquid chromatography (HPLC) assay (National Jewish Medical and Research Center, Denver, CO, or Mayo Clinic Department of Laboratory Medicine and Pathology, Rochester, MN).

Assessment of posaconazole-associated toxicity. Toxicity was defined according to the Common Terminology Criteria for Adverse Effects (CTCAE) version 4.03 (15). All patients were monitored for the occurrence of hepatotoxicity with liver function tests obtained at least twice a week while receiving PCZ prophylaxis. Grade 2 or higher hepatotoxicity was defined as an increase in alanine transaminase (ALT) to 3 times the upper limit of normal and a 30% increase in the baseline value while receiving PCZ prophylaxis (15). QT prolongation was not routinely monitored with an electrocardiogram (ECG) unless clinically indicated. Electrocardiograms performed on patients while receiving PCZ were reviewed, and a corrected QT (QTc) interval of >480 ms was considered clinically significant (grade 2 or higher) (15).

Assessment of breakthrough infections. While not a primary outcome of this therapeutic drug monitoring study, the occurrence of breakthrough fungal infections in patients was evaluated. For suspected pneumonia, serum samples for measurement of levels of fungal markers (galactomannan and/or 1,3-β-D-glucan assay) and chest computed tomography (CT) scans were obtained, along with bronchoalveolar lavage (BAL) fluid samples, as indicated. Galactomannan levels were also measured in the BAL fluid samples, when possible. Routine surveillance of serum fungal markers was not performed without a clinical suspicion of a fungal infection. Blood and sterile cultures positive for yeast or *Candida* species were considered indicators of breakthrough infections. Standard definitions of invasive fungal infections were used to determine breakthrough fungal infections (16).

RESULTS

Patient characteristics. The baseline characteristics of all 150 patients stratified into 2 groups, PCZ-susp ($n = 118$) and PCZ-tab ($n = 32$), are described in Table 1. The two groups were similar for all baseline variables considered, including age, gender, diagnosis, body mass index, nutritional status, presence of vomiting/diarrhea/mucositis, chemotherapy regimen, and concomitant acid suppressant use ($P > 0.05$).

TABLE 1 Patient characteristics

Characteristic	Suspension patients ($n = 118$)	Tablet patients ($n = 32$)	P
Age (yr) (median [range])	57 (18–84)	52 (20–75)	0.22
Male gender (no. [%])	59 (50)	17 (53)	0.84
Weight (kg) (median [range])	84 (38–175)	90 (61–194)	0.13
BMI[a] (kg/m^2) (median [range])	30 (15–65)	29.8 (22–59)	0.75
BMI of >30 g/m^2 (no. [%])	58 (49)	16 (50)	0.99
Diagnosis (no. [%])			
Acute myeloid leukemia	115 (97)	30 (94)	0.29
MDS[b]	3 (3)	2 (6)	
Chemotherapy regimen (no. [%])			
Cytarabine-anthracycline (7 + 3)	80 (68)	23 (72)	
High-dose cytarabine based	14 (12)	0 (0)	
Clofarabine based	8 (7)	4 (13)	0.18
Mitoxantrone-etoposide	5 (4)	2 (6)	
Other	11 (9)	3 (9)	
Mucositis (no. [%])	23 (19)	4 (13)	0.45
Diarrhea (no. [%])	24 (20)	6 (19)	0.99
Vomiting (no. [%])	14 (12)	5 (16)	0.56
Nutritional status (no. [%])			
Category 1	43 (36)	19 (59)	
Category 2	41 (35)	10 (31)	0.13
Category 3	18 (15)	2 (6)	
Unknown	16 (14)	1 (3)	
Acid suppression (no. [%])			
Proton pump inhibitor	44 (37)	11 (34)	
H2 antagonist	69 (58)	21 (66)	0.62
None	5 (4)	0 (0)	

[a] BMI, body mass index.
[b] MDS, myelodysplastic syndrome.

Posaconazole concentrations. After initiation of PCZ, serum concentration measurements were obtained at a median of 8 days (range, 7 to 19 days) in the PCZ-susp group and 7 days (range, 7 to 12 days) in the PCZ-tab group. The median C_{ss} values in the PCZ-susp and PCZ-tab groups were 390 ng/ml (range, 51 to 1,870 ng/ml; mean, 463 ± 309 ng/ml) and 1,740 ng/ml (range, 662 to 3,350 ng/ml; mean, 1,740 ± 706 ng/ml), respectively ($P < 0.0001$). Figure 1 illustrates the C_{ss} distributions in the two groups. The percentages of patients achieving the target goal level of ≥700 ng/ml were 17% ($n = 20$) versus 97% ($n = 32$) in the two groups, respectively ($P < 0.001$). By univariate analysis, only poor nutritional status (category 3) adversely affected the PCZ concentrations (Table 2).

To assess the effect of concomitant PPI or H2A agents, we included an interaction term in the multivariate linear regression model to determine if there is an association and found it to be statistically significant ($P = 0.001$), which implies that the PCZ concentration was significantly different when it was stratified by the type of acid suppression (PPI or H2A) between the suspension and tablet groups. In particular, the mean PCZ concentration in

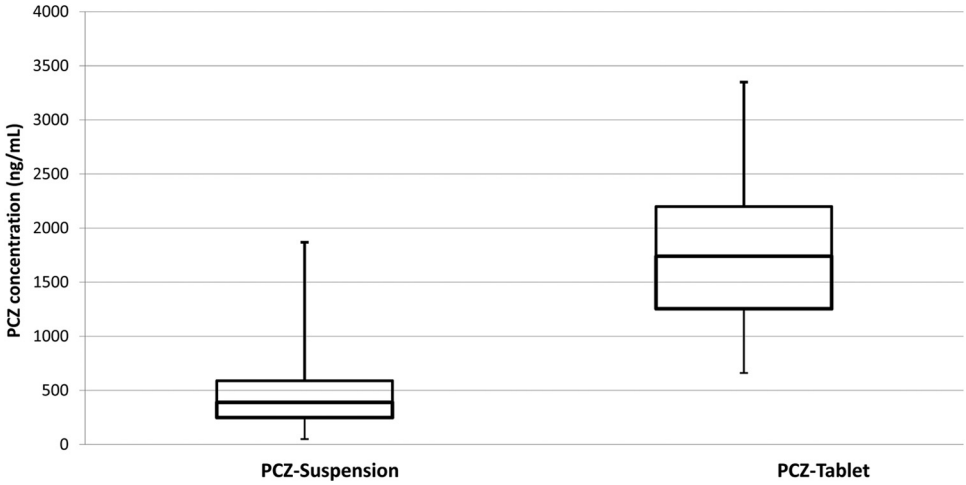

FIG 1 Box plot of PCZ serum concentrations by treatment group ($P < 0.0001$).

the suspension group was lower in the PPI patients (403 ng/ml) than in the H2A patients (510 ng/ml), while the mean PCZ concentration in the tablet group was higher in the PPI patients (2,095 ng/ml) than in the H2A patients (1,617 ng/ml) (Fig. 2).

Toxicity and breakthrough infections. Clinically significant hepatotoxicity occurred in only 1 patient in each group (both grade 2), and both were thought to be related to PCZ. The PCZ-susp patient had a C_{ss} of 390 ng/ml, and the PCZ-tab patient had a C_{ss} of 3,350 ng/ml, which was the highest concentration in the tablet patient group. Measurements of the QTc interval with ECG during therapy were available for 32 patients in the PCZ-susp group and for 12 patients in the PCZ-tab group. Of these, clinically significant (grade 2 or higher) prolongations were noted in 9% ($n = 3$) and 17% ($n = 2$) in the PCZ-susp and PCZ-tab groups, respectively ($P = 0.6$). While 1 patient in each group had grade 3 QTc prolongation, no grade 4 prolongation or arrhythmia was noted in any patients. The PCZ C_{ss} values were 231, 426, and 1,200 ng/ml in the three PCZ-susp patients with a prolonged QTc interval and were 2,090 and 2,190 ng/ml in the two PCZ-tab patients with a prolonged QTc interval.

Breakthrough fungal infections were documented in 7% ($n = 8$) and 3% ($n = 1$) in the PCZ-susp and PCZ-tab groups, respectively ($P = 0.68$). In the PCZ-susp group, breakthrough infections were classified as proven in 3 cases (2 patients with *Candida glabrata* and 1 patient with *Alternaria* species and concomitant galactomannan-positive BAL fluid), as probable in 1 patient, and as possible in 4 patients. The median PCZ C_{ss} for these 8 patients was 382 ng/ml (range, 190 to 741 ng/ml). The breakthrough infection in the patient in the PCZ-tab group was documented as possible. This patient had a CT scan showing a large pulmonary nodule, which was unresponsive to broad-spectrum antibiotics. His serum galactomannan and 1,3-β-D-glucan assays were both negative, and he also underwent bronchoalveolar lavage with negative cultures and galactomannan assay. His PCZ C_{ss} was 2,350 ng/ml.

TABLE 2 Linear regression models of the relation between PCZ serum concentration and treatment group, age, body mass index, mucositis, diarrhea, vomiting, nutrition status, and acid suppression

Characteristic	PCZ concn effect[a] (SE)	*P*
PCZ treatment group		
Tablet	1,318 (85)	<0.0001
Suspension	Ref[b]	
Age	3 (4)	0.45
Gender (male)	18 (113)	0.88
BMI[c] of >30 kg/m^2	68 (112)	0.55
Mucositis	−194 (146)	0.19
Diarrhea	−179 (140)	0.20
Vomiting	19 (169)	0.91
Nutrition status		
Category 1	Ref	
Category 2	−183 (133)	0.17
Category 3	−439 (181)	0.02
Acid suppression		
Proton pump inhibitor	Ref	
H2 antagonist	27 (118)	0.82
None	−407 (321)	0.21

[a] Effect, estimated mean difference.
[b] Ref, reference.
[c] BMI, body mass index.

DISCUSSION

In this study, 150 patients with high-risk myeloid malignancies undergoing inpatient chemotherapy and receiving PCZ as antifungal prophylaxis were included. Noting that the baseline characteristics were similar in both groups, in this report, we clearly show superior C_{ss} with the use of the delayed-release PCZ-tab compared to that with the PCZ-susp, likely due to better absorption and oral bioavailability of the tablets. The serum steady-state concentrations and the percentage of patients achieving the target therapeutic concentrations (≥700 ng/ml) were significantly higher in the PCZ-tab group. Notwithstanding the higher C_{ss} in PCZ-tab group, the toxicities did not appear different between the groups. This might be explained by the relatively smaller sample size in the PCZ-tab group and the lack of uniform ECG monitoring in all patients and needs to be evaluated further in a larger patient cohort. To the best of our knowledge, this is the largest comparative clinical study to date evaluating the 2 oral formula-

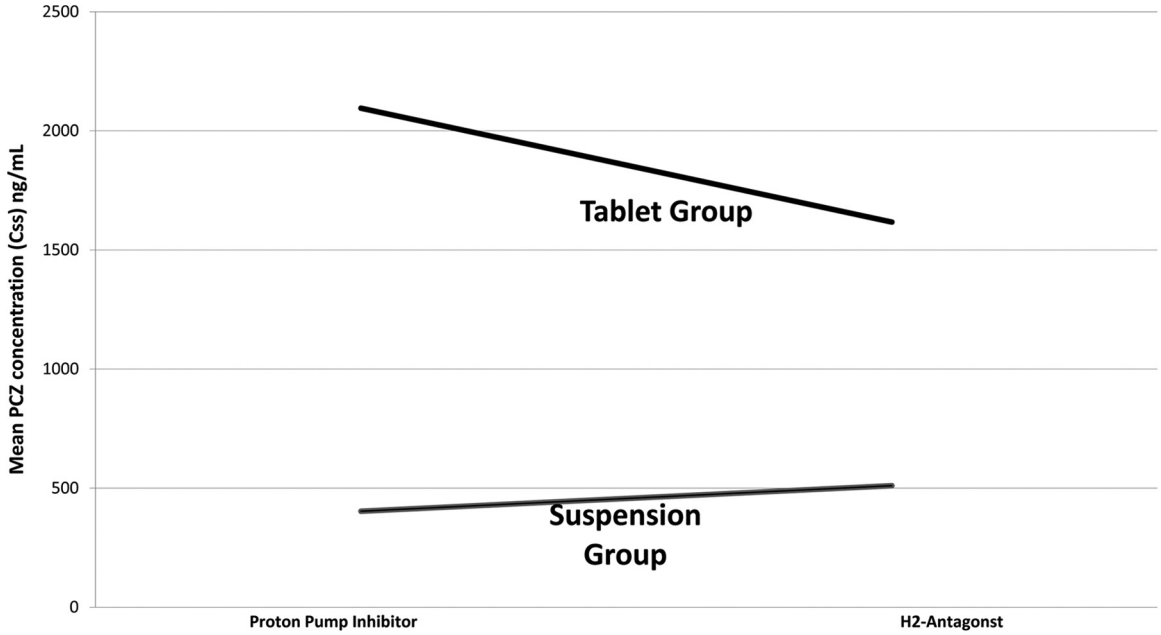

FIG 2 Linear regression model of PCZ concentrations stratified by acid suppression and treatment group. The PCZ concentration was significantly different when it was stratified by acid suppression (PPI or H2A) and treatment group (suspension or tablet) with a *P* value of 0.001 from the interaction term in the linear regression model. In particular, the median PCZ concentration in the suspension group was lower in PPI patients (330 ng/ml) than in H2A patients (410 ng/ml), while the median PCZ concentration in the tablet group was higher in PPI patients (2,190 ng/ml) than in H2A patients (1,470 ng/ml).

tions of PCZ. In the only other published report, Jung et al. (17) evaluated crossover in 12 leukemia patients from the PCZ suspension to the tablet form and found better PCZ exposure without significant toxicity with the PCZ-tab, similar to our data.

We assessed the interactions between the PCZ formulation and concomitant acid suppressant therapy and found significantly higher PCZ drug levels with the tablet formulation irrespective of the type of acid suppressant used. In line with other reports (8–11), our study suggests limited effects on bioavailability and drug-drug interactions with concomitant acid suppression and the PCZ-tab, most likely related to the enhanced delivery system of the PCZ-tab and the delayed-release formulation. This has very important clinical implications since stress ulcer prophylaxis is often considered in this clinical setting due to the gastrointestinal effects of cytotoxic agents and concomitant thrombocytopenia.

It may be noted that in the PCZ-susp cohort, the dosing range was 600 to 800 mg/day (200 mg three times daily or 400 mg twice daily). The 800-mg/day dose (higher than the FDA-approved prophylaxis dose) was institutionally implemented when the first 21 patients receiving 600 mg/day of PCZ suspension had subtherapeutic levels (median, 400 ng/ml; range, 100 to 860; mean, 377 ng/ml). The subsequent 97 patients all received 400 mg of PCZ-susp orally twice daily, resulting in a median C_{ss} of 390 ng/ml (range, 51 to 1,870; mean, 482 ng/ml). Despite the higher daily dose of PCZ-susp, our data show substantially inferior C_{ss} with PCZ-susp than with PCZ-tab, thus reiterating the importance of the formulation in achieving adequate drug levels.

Two patients included in the analysis had previously received the PCZ-susp and subsequently received the PCZ-tab. The first patient had a PCZ C_{ss} of 260 ng/ml when receiving the suspension formulation and their concentration increased to 1,070 ng/ml after switching to the tablets. The second patient increased from a PCZ C_{ss} of 567 ng/ml to a concentration of 1,980 ng/ml with the PCZ-tab.

In conclusion, in this retrospective analysis, the PCZ-tab formulation was associated with improved absorption, leading to better C_{ss} and a higher probability of achievement of therapeutic goals than with the suspension without significantly affecting toxicities and breakthrough infections. Also noted in our study was the finding that concomitant PPI use did not affect the absorption or C_{ss} of PCZ tablets. While additional studies in larger patient cohorts are needed to confirm our results, given that no prospective head-to-head comparative studies of these two formulations are available or likely to be performed in the near future, we conclude that the delayed-release tablet formulation seems to be the better option for antifungal prophylaxis in patients with high-risk myeloid malignancies.

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We declare no conflicts of interest.

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