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

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Abstract:

Posaconazole (PCZ), approved for prophylaxis against invasive fungal disease in high-risk patients, is commercially available orally as a suspension formulation (PCZ-susp) and a delayed-release tablet (PCZ-tab). We evaluated the serum steady state concentrations (C_{ss}) of PCZ stratified by 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 $\geq$ 700 ng/mL. Secondary outcomes included toxicity assessment (hepatotoxicity and QTc prolongation) and breakthrough fungal infections. Patients who received 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 - 1870 ng/ml; mean: 436 ng/mL), compared to 1740 ng/mL (range: 662 - 3350 ng/ml; mean: 1781 ng/mL) in the PCZ-tab group (P<0.0001). The percentage of patients achieving target goal of ≥700 ng/mL was 17% versus 97%, respectively (P<0.0001). Hepatotoxicity ($\geq$ grade 2) occurred in 1 patient in each group. QTc measurements were available in 32 patients in PCZ-susp and 12 patients in the PCZ-tab group and prolonged interval of grade 2 or more was 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 use of PCZ-tab was associated with higher C_{ss} as well as probability of achieving therapeutic goals without worsening adverse effects.

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Background

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 suspension (PCZ-susp) and delayed-release tablets (PCZ-tab).[1] Several studies have shown that the gastrointestinal absorption and bioavailability of PCZ-susp is unpredictable and dependent on various factors including food intake and concomitant acid suppressants.[2-7] Due to 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 PCZ-susp occurring at 800 mg/day.[12] Current guidelines recommend a goal steady state concentrations (Css) $\geq$ 700 ng/mL in the prophylaxis setting.[13] Comparative studies evaluating PCZ-susp and the newer PCZ-tab are not available. Here in, 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 expected nadir ANC <500/μL and duration of ≥7-10days), and receiving PCZ prophylaxis were included. Patients received PCZ-susp (600-800 mg/day) between February 2008 and December 2013 and PCZ-tab (300mg twice

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daily on Day1, then 300mg once daily) between January 2014 to December 2014. Serum PCZ concentrations were routinely done at our institution after at least 7 days of therapy to allow the drug to reach C_{ss}. 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; 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 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) as well as breakthrough fungal infections in each group. Of note, QTc prolongation was not routinely assessed in our patients, and was only reported in patients receiving evaluation. The potential impact of age, obesity, nutritional supplementation, diarrhea, vomiting, mucositis, and concomitant use of acid suppressing medications [proton-pump inhibitors (PPI) and histamine antagonists (H2A)] on PCZ C_{ss} were also evaluated.

Food intake and nutritional supplementation was 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 who consumed 50-75% of meals or 1-2 nutritional supplements/day; and category 3 who consumed < 50% of meals or had no nutritional supplements/day.

Statistical Analysis:

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Descriptive statistics were used to summarize baseline patient characteristics. Categorical data were described using contingency tables. Continuous variables were summarized using mean with standard deviation or median with range. Fisher's exact test was used to assess the independence between two categorical variables and Wilcoxon rank sum test was used to assess difference between the 2 groups for continuous variables. Linear regression models were performed to assess PCZ concentrations for potential impact 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 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 hours 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 assessments were defined according to common terminology criteria of adverse

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effects (CTCAE) version 4.03.[15] All patients were monitored for occurrence of hepatotoxicity while on PCZ prophylaxis with liver function tests obtained at least twice a week. 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 of baseline value while on PCZ prophylaxis.[15] QT prolongation was not routinely monitored with electrocardiogram (ECG) unless clinically indicated. Electrocardiograms performed on patients while on PCZ were reviewed and a QTc interval >480 ms was considered clinically significant (≥ grade 2).[15]

Assessment of Breakthrough Infections:

While not a primary outcome of this therapeutic drug monitoring study, patients were evalauted for breakthrough fungal infections. For suspected pneumonia, serum fungal makers (galactomannan +/- 1,3-β-D-Glucan assay) and chest computed tomography (CT) were obtained, along with bronchoalveolar lavage (BAL), as indicated. Galactomannan levels were also sent from the BAL collection, when possible. Routine surveillance of fungal serum markers was not performed without clinical suspicion of a fungal infection. Blood and sterile cultures positive for yeast or *Candida* species were considered as breakthrough infections. Standard definitions of invasive fungal infections were used to determine breakthrough fungal infections.[16]

Results:

Patient Characteristics:

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

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vomiting/diarrhea/mucositis, chemotherapy regimen and concomitant acid suppressant use (P>0.05).

Posaconazole Concentration:

After initiation of PCZ, serum concentration measurements were obtained at a median of 8 days (range: 7-19) in the PCZ-susp group and 7 days (range: 7-12) in the PCZ-tab group. The median C_{ss} in the PCZ-susp and PCZ-tab groups were 390 ng/ml (range: 51 - 1870 ng/ml; mean: 463 +/- 309 ng/ml) and 1740 ng/ml (range: 662 - 3350 ng/ml; mean: 1740 +/- 706 ng/ml), respectively ($P < 0.0001$). Figure 1 illustrates the C_{ss} distributions in the two groups. The percentage of patients achieving the target goal level $\geq$ 700 ng/ml was 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 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 PCZ concentration was significantly different when it was stratified by type of acid suppression (PPI or H2A) between suspension and tablet groups. In particular, the mean PCZ concentration in the suspension group was lower in the PPI patients (403 ng/ml) than H2A patients (510 ng/ml), while the mean PCZ concentration in the tablet group was higher in the PPI patients (2095 ng/ml) than H2A patients (1617 ng/ml) (Figure 2).

Toxicity and Breakthrough Infections:

Clinically significant hepatotoxicity occurred in only 1 patient in each group (both grade 2), 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 Css of 3350 ng/ml, which was the highest concentration in the tablet

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patient group. Measurement of QTc with ECG during therapy was available in 32 patients in PCZ-susp group and 12 in the PCZ-tab group. Of these, clinically significant (≥ grade 2) prolongation was 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. PCZ C_{ss} were 231, 426, and 1200 ng/ml in the three PCZ-susp patients with prolonged QTc; and were 2090 and 2190 ng/ml in the two PCZ-tab patients with prolonged QTc.

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 (two patients with *Candida glabrata*; one patient with *Alternia* species and comcomitant galactomannan-postive BAL), as *probable* in 1 and as *possible* in 4 patients. The median PCZ C_{ss} for these 8 patients was 382 ng/ml (range 190 -741 ng/ml). The breakthrough infection in the patient in PCZ-tab group was documented as *possible*. This patient had a CT scan with a large pulmonary nodule, unresponsive to broad spectrum antibiotics. His serum galactomannan and 1,3-β-D-Glucan assay were both negative, and he also underwent bronchoalveolar lavage with negative cultures and galactomannan assay. His PCZ C_{ss} was 2350 ng/ml.

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, this report clearly shows superior C_{ss} with the use of delayed-release PCZ-tab compared to PCZ-susp, likely due to better absorption and

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oral bioavailabilty of the tablets. The serum steady state concentrations, as well as the percentage of patients achieving target therapeutic concentrations (≥ 700 ng/ml), were significantly higher in PCZ-tab group. Notwithstanding the higher C_{ss} in PCZ-tab group, the toxicities did not appear different between the groups. This could be explained by the relatively smaller sample size in the PCZ-tab group and that ECG monitoring was not uniformly conducted in all patients and will need 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 formulations of PCZ. In the only other published report, Jung et al.[17] evaluated crossover in 12 leukemia patients from PCZ-susp to tablet form and found better PCZ exposure without significant toxicity with PCZ-tab, similar to our data.

We assessed the interactions between 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 effect on bioavailability and drug-drug interaction with concomitant acid suppression and PCZ-tab. This is 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 600-800 mg/day (200mg thrice daily or 400mg twice daily). The 800mg/day dose (higher than the FDA approved prophylaxis dose) was institutionally implemented when the first 21 patients receiving 600mg/day of PCZ suspension had sub-therapeutic levels (median: 400 ng/ml [range 100-860]; mean: 377 ng/ml). The subsequent 97 patients all received 400mg PO twice daily of PCZ-susp

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resulting in a median C_{ss} of 390 ng/ml (range 51 – 1870); mean: 482 ng/ml. In spite of the higher daily dose of PCZ-susp, our data show substantially inferior C_{ss} with PCZ-susp compared to PCZ-tab, thus reiterating the importance of formulation in achieving adequate drug levels.

Two patients were included in the analysis that had previously received PCZ-susp and subsequently received PCZ-tab. The first patient had a PCZ C_{ss} of 260 ng/ml when receiving the suspension formulation and increased their concentration to 1070 ng/ml after switching to the tablets. The second patient increased from a PCZ C_{ss} of 567 ng/ml to a concentration of 1980 ng/ml with PCZ-tab.

Conclusions:

In this retrospective analysis, PCZ-tab formulation was associated with improved absorption leading to better C_{ss} and higher probability of achieving therapeutic goals compared to the suspension without significantly affecting toxicities and breakthrough infections. Also noted in our study was that concomitant PPI use did not affect 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, delayed-release tablet formulation seems to be the better option for antifungal prophylaxis in high-risk myeloid malignancies.

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309 **Table 1.** Patient Characteristics

	Suspension Patients (n=118)	**Tablet Patients (n=32)**	**P-value**
Median age, years (range)	57 (18-84)	52 (20-75)	0.22
Male gender	59 (50%)	17 (53%)	0.84
Median weight, kg (range)	84 (38-175)	90 (61-194)	0.13
BMI	30 (15-65)	29.8 (22-59)	0.75
BMI > 30	58 (49%)	16 (50%)	0.99
Diagnosis			
Acute myeloid leukemia	115 (97%)	30 (94%)	0.29
MDS	3 (3%)	2 (6%)	
Chemotherapy regimen			
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	23 (19%)	4 (13%)	0.45
Diarrhea	24 (20%)	6 (19%)	0.99
Vomiting	14 (12%)	5 (16%)	0.56

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Nutritional status			
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			
Proton Pump Inhibitor	44 (37%)	11 (34%)	
H2-antagonist	69 (58%)	21 (66%)	0.62
None	5 (4%)	0 (0%)	

Abbreviations: BMI – body mass index, MDS – myelodysplastic syndrome

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313 **Table 2.** Linear regression models of the relation between PCZ serum concentration and
314 treatment group, age, BMI, mucositis, diarrhea, vomiting, nutrition status, and acid suppression.

	PCZ concentration	
	Effect (SE)	**P-value**
PCZ treatment group		
Tablet	1318 (85)	<0.0001
Suspension	REF	
Age	3 (4)	0.45
Gender (Male)	18 (113)	0.88
BMI > 30	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-blocker	27 (118)	0.82
None	-407 (321)	0.21

315 Abbreviations: Effect – Estimated mean difference, SE – Standard Error, REF – Reference, BMI

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316 – body mass index

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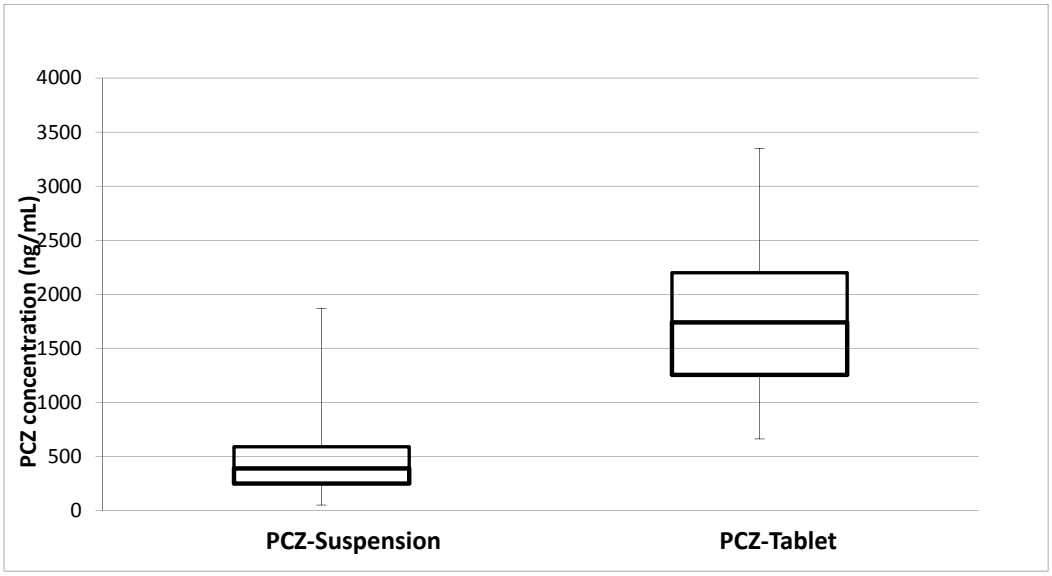

Figure 1. Box plot of PCZ serum concentrations by treatment group (P>0.0001)

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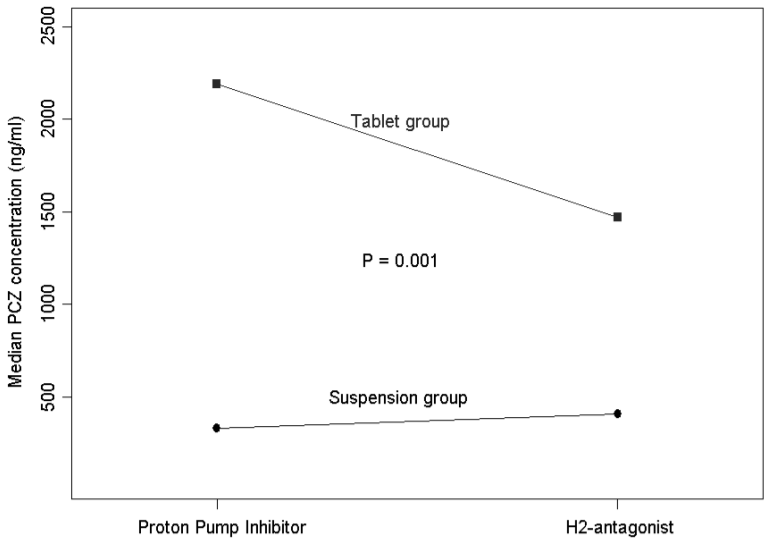

Figure 2. PCZ concentration was significantly different when it was stratified by acid suppression (PPI or H2A) and treatment group (suspension or tablet) with p = 0.001 from the interaction term in the linear regression model. In particular, the median PCZ concentration in the suspension group was lower in PPI patients (330 ng/ml) than H2A (410 ng/ml), while the median PCZ concentration in the tablet group was higher in PPI (2190 ng/ml) than H2A (1470 ng/ml).

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