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Retrospective Comparison of Posaconazole Levels in Patients Taking the Delayed-Release Tablet versus the Oral Suspension

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While posaconazole prophylaxis decreases the risk of invasive fungal infection compared to fluconazole, low bioavailability of the oral-suspension formulation limits its efficacy. A new delayed-release tablet formulation demonstrated an improved pharmacokinetic profile in healthy volunteers. However, serum levels for the two formulations have not been compared in clinical practice. This study compared achievement of therapeutic posaconazole levels in patients taking the delayed-release tablet to those taking the oral suspension. This retrospective cohort study included 93 patients initiated on posaconazole between 2012 and 2014 and had at least one serum posaconazole level measured. The primary measure was the proportion of patients achieving an initial therapeutic level (>700 ng/ml). An initial therapeutic posaconazole level was seen in 29 of 32 (91%) patients receiving tablets and 37 of 61 (61%) patients receiving suspension ($P = 0.003$). Among patients with a steady-state level measured 5 to 14 days after initiation, a therapeutic level was observed in 18 of 20 (90%) patients receiving tablets and 25 of 43 (58%) patients receiving suspension ($P = 0.01$). In these patients, the median posaconazole level of the tablet cohort (1655 ng/ml) was twice that of the suspension cohort (798 ng/ml) ($P = 0.004$). In this cohort study, the improved bioavailability of delayed-release posaconazole tablets translates into a significantly higher proportion of patients achieving therapeutic serum levels than in the cohort receiving the oral suspension. The results of this study strongly support the use of delayed-release tablets over suspension in patients at risk for invasive fungal infection.

Patients with hematologic malignancies and solid organ transplants are at risk of invasive fungal infection (IFI), and prolonged neutropenia may increase the risk of IFIs that are not prevented by fluconazole. Posaconazole oral suspension, an oral triazole active against molds, was approved by the Food and Drug Administration (FDA) in 2006 for IFI prophylaxis in patients with prolonged neutropenia after studies demonstrated improved efficacy and overall survival compared to fluconazole or itraconazole (1, 2).

Despite the approval of posaconazole for this indication, the oral suspension has limited bioavailability, particularly when decreased oral intake, mucositis, gastrointestinal graft-versus-host disease (GVHD), or diarrhea is present (3). Given that subtherapeutic posaconazole levels may be associated with breakthrough IFIs (4) and decreased likelihood of successful treatment (5), a new delayed-release (DR) tablet formulation with higher oral bioavailability (6) holds promise. In fact, a phase 3 trial reports that over 99% of patients with hematologic malignancies receiving DR tablets achieved levels of >500 ng/ml (7). Aside from a crossover study of 12 leukemia patients (8), clinical practice data comparing serum concentrations of the two posaconazole formulations have not been reported.

The primary objective of this study was to compare steady-state levels of serum posaconazole in patients taking DR posaconazole tablets to those taking oral suspension to determine if the pharmacokinetic advantage of DR tablets observed in healthy volunteers and clinical trials translates to a higher rate of therapeutic serum concentrations in clinical practice.

MATERIALS AND METHODS

Study population. This study was approved by the institutional review board at Mayo Clinic. All patients who were initiated on posaconazole and had a serum posaconazole level measured from January 2012 to July 2014 were included. Only patients who had consented to participate in research at Mayo Clinic were eligible. Posaconazole was prescribed or recommended by an infectious disease or hematology physician, as part of institutional recommendations. Delayed-release tablets were added to the formulary in April 2014, so all patients in the DR cohort were treated in 2014, while 58 out of 61 patients in the suspension cohort were treated in 2012-2013. Therapeutic drug monitoring was performed routinely for patients on posaconazole, although timing of monitoring and dosing of the oral suspension were at the physician's discretion. Patients with a level measured within 5 to 14 days after posaconazole initiation formed the primary study population. This range was based on previous pharmacokinetic studies that showed that steady-state levels can be achieved as early as 5 days from initiation (9), and it was felt that levels obtained within 14 days from initiation provided clinically useful data for patient care. Patients who had a level determined before 5 days or after 14 days from initiation were included in a secondary analysis. Patients were excluded if they switched formulations before a level was determined. Patients were divided into two cohorts: those initiated on DR tablets and those initiated on oral suspension.

Posaconazole level measurement. Blood samples were collected in Vacutainer tubes, allowed to clot, centrifuged, and then poured off for

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TABLE 1 Characteristics of patients prescribed posaconazole[a]

Characteristic[b]	DR tablet ($n = 20$)	Suspension ($n = 43$)	P[d]
Median age (IQR)	55.5 (46.6–62.9)	55.8 (43.7–61.4)	0.802
Male gender	12 (60.0)	26 (60.5)	0.972
Inpatient status at initiation	10 (50)	18 (41.9)	0.545
Possible, probable, or proven IFI at initiation	9 (45)	31 (72.1)	0.038
Regular diet status for >50% of time from initiation to first level	20 (100)	41 (95.4)	0.327
Post-stem cell transplant (allogeneic)	7 (35)	14 (32.6)	0.848
Hematologic malignancy	13 (65)	28 (65.1)	0.993
Acute myeloid leukemia	8 (40)	10 (23.3)	
Chronic lymphocytic leukemia	1 (5)	8 (18.6)	
Acute lymphocytic leukemia	1 (5)	0	
Chronic myeloid leukemia	1 (5)	3 (7)	
Lymphoma	1 (5)	3 (7)	
Multiple myeloma	0	1 (2.3)	
Other	1 (5)	3 (7)	
Solid organ transplant	4 (20)	12 (27.9)	0.502
Lung	2 (10)	6 (14)	
Liver	0	1 (2.3)	
Kidney	1 (5)	2 (4.7)	
Heart/lung	0	1 (2.3)	
Heart/kidney	0	1 (2.3)	
Kidney/pancreas	0	1 (2.3)	
Liver/lung	1 (5)	0	
Acid suppression	20 (100)	34 (79.1)	0.027
PPI	20 (100)	29 (67.4)	
H2 blocker	0	5 (11.6)	
Other interacting medications[c]	1 (5)	0 (0)	0.139
Diarrhea	3 (15)	10 (23.3)	0.451
Mucositis	2 (10)	2 (4.7)	0.418
Gastrointestinal GVHD			0.716
Acute	2 (10)	2 (4.7)	
Chronic	1 (5)	2 (4.7)	
Neutropenia	4 (20)	11 (25.6)	0.628
Concomitant use of another antifungal	7 (35)	25 (58.1)	0.087

[a] Values are numbers and percentages unless otherwise noted.
[b] IQR, interquartile range; IFI, invasive fungal infection; GVHD, graft-versus-host disease.
[c] The only interacting medication recorded was metoclopramide.
[d] P values derived using Pearson's chi-squared test for categorical variables and Wilcoxon rank sum test for continuous variables.

analysis. The posaconazole concentrations were determined using an unpublished, laboratory-developed liquid chromatography-tandem mass spectrometry (LC-MS/MS) test, validated by our institution in a manner consistent with Clinical Laboratory Improvement Amendments (CLIA) requirements. Patient serum samples, standards, controls, and a blank sample (100 μl) were mixed with acetonitrile (300 μl) containing the internal standard (posaconazole-d4), vortexed, and centrifuged to precipitate the proteins. The supernatant was then injected (20 μl) into the LC-MS/MS for analysis. The analytical measuring range of the assay was from 50 to 5,000 ng/ml. The target mean and coefficient of variation for each of the three quality control samples were 279 ng/ml (5.1%), 830 ng/ml (4.3%), and 4,065 (4.3%).

Outcome measures. The primary outcome was the proportion of initial therapeutic posaconazole levels, defined as an initial level greater than 700 ng/ml, based on previous literature (5, 10). A secondary outcome was the proportion of levels greater than 1,250 ng/ml. Median initial levels were also compared. Other characteristics were analyzed to account for factors influencing absorption, such as acid suppressants, mucositis, diet type, diarrhea, and gastrointestinal graft-versus-host disease (GVHD) (11). Diarrhea was recorded per the researcher's clinical judgment of the medical records. The proportion of patients taking phenytoin, metoclopramide, efavirenz, bosutinib, fosamprenavir, rifampin/rifabutin, or cobicistat was also recorded, given the interactions between posaconazole and these medications (12).

Statistical analysis. All data were entered into a RedCap database (Vanderbilt University, Nashville, TN, USA). JMP 10.0 statistical software (SAS Institute, Cary, NC, USA) was used for statistical analysis. Pearson's chi-squared and Wilcoxon rank sum tests were used for categorical variables and continuous variables, respectively.

RESULTS

Study cohort. A total of 94 patients meeting inclusion criteria were evaluated for the study. One patient was excluded because he

TABLE 2 Initial posaconazole levels among patients with levels measured between 5 and 14 days and any time after posaconazole initiation[a]

Group and parameter	DR tablet	Suspension	P^b
Patients with initial levels determined 5 to 14 days after posaconazole administration	$n = 20$	$n = 43$	
Days from initiation to first level (IQR)	10 (6–13)	8 (6–12)	0.424
Median level (IQR)	1,655 (1,080–2250)	798 (572–1,500)	0.004
No. (%) >700 ng/ml	18 (90)	25 (58)	0.011
No. (%) >1,250 ng/ml	15 (75)	14 (32.6)	0.002
Entire cohort regardless of when initial posaconazole levels were drawn	$n = 32$	$n = 61$	
Days from initiation to first level (IQR)	11.5 (7–19)	8 (7–15)	0.303
Median level (IQR)	1,620 (957–2,258)	967 (590–1,420)	<0.001
No. (%) >700 ng/ml	29 (90.6)	37 (60.7)	0.003
No. (%) >1,250 ng/ml	20 (62.5)	19 (31.1)	0.004

[a] IQR, interquartile range; DR, delayed release.
[b] *P* values derived using Pearson's chi-squared test for categorical variables and Wilcoxon rank sum test for continuous variables.

switched formulations before a drug level was obtained, leaving a study population of 93 patients. Thirty-two patients (34%) were in the DR tablet cohort, and 61 patients (66%) were in the oral-suspension cohort.

There were 63 patients who had an initial level measured between 5 and 14 days of posaconazole initiation. Within this group, 48 follow-up posaconazole concentrations were also collected. Within the oral-suspension cohort of 43 patients, 16 patients (37.2%) received 200 mg four times a day, 12 patients (27.9%) received 200 mg three times a day, and 15 patients (34.9%) received 400 mg twice a day. All 20 patients initiated on the DR tablet were given a loading dose (300 mg twice on the first day) and then 300 mg daily. Baseline conditions within this group did not differ substantially between the two cohorts (Table 1). However, the DR tablet was less frequently prescribed as therapy for IFI rather than prophylaxis, compared to the oral suspension (45% versus 72%; $P = 0.038$). Acid-suppressive medication use was more common in the DR tablet cohort (100% versus 79%; $P = 0.027$).

Based on scatterplot analysis, initial levels of posaconazole did not vary significantly by the number of days from initiation to level ($R^2 = 0.015$; $P = 0.333$). However, median posaconazole concentration determined between 8 and 14 days was significantly higher than the median concentration determined between 5 and 7 days (1,310 ng/ml versus 943 ng/ml; $P = 0.0433$). Follow-up levels were higher in both the group with initial levels determined between 5 and 7 days (1,065 ng/ml; interquartile range [IQR], 385 to 1,605 ng/ml) and the group with initial levels determined between 8 and 14 days (1,425 ng/ml; IQR, 1,043 to 2,180 ng/ml). The proportions of levels determined between 5 and 7 days versus 8 and 14 days were not significantly different between the oral-suspension and delayed-release cohorts (53% versus 65%; $P = 0.39$). The median difference between the initial level and follow-up level for the entire cohort ($n = 48$) was 175 ng/ml (IQR = −121 to 495). The number of days between the first and second levels ranged from 0 to 94, with a median of 12.5.

Primary and secondary endpoints. Among the 63 patients with levels determined between 5 and 14 days, the DR tablet cohort had a significantly higher proportion with a posaconazole concentration greater than 700 ng/ml (90% versus 58%; $P = 0.011$) and 1,250 ng/ml (75% versus 33%; $P = 0.002$) than the oral-solution cohort (Table 2). The median posaconazole concentration was also significantly higher in the DR tablet cohort than the oral-suspension cohort (1655 versus 798 ng/ml; $P = 0.004$). Similarly, when all 93 patients were included (including the 30 patients whose initial posaconazole levels were determined outside the 5- to 14-day interval), the DR tablet cohort more commonly achieved the prespecified therapeutic thresholds (Table 2). Within the group of 93 patients, there were no significant differences between the three patients in the DR cohort who did not achieve a therapeutic level and the rest of the cohort. Nontherapeutic posaconazole levels in oral-suspension patients ranged from 55 to 688 ng/ml. These patients also did not differ significantly from the other oral-suspension patients in terms of diarrhea, mucositis, or GVHD. Among the 63 patients with levels determined within 5 to 14 days of initiation, there was also no difference between the patients who did not achieve a therapeutic level and those who did.

DISCUSSION

We demonstrated that patients initiated on posaconazole in the form of a DR tablet were more likely to achieve a level greater than 700 and 1,250 ng/ml than patients on posaconazole in the form of an oral suspension. In addition, median levels were almost twice as high in the DR tablet cohort. Although previous studies evaluated the two formulations individually, this is the first study to directly compare steady-state levels of the two posaconazole formulations in routine clinical practice. Our findings complement studies describing the pharmacokinetics of the two posaconazole formulations (6, 13) by demonstrating that the improved pharmacokinetic profile of the DR tablet does translate into higher steady-state levels in a clinical-practice setting.

Our results are supported by previous studies looking at the individual formulations. One study of the oral suspension found steady-state levels (810 ng/ml) and a proportion (57%) achieving a therapeutic level (>700) that were similar to our results (3). Another study of patients using the DR tablets also had results similar to ours, with 97% achieving a therapeutic level (13). However, therapeutic levels in that particular study were defined as ≥500 ng/ml, and it was a phase 1b clinical trial rather than a routine clinical practice setting (13). Additionally, neither of these studies actually compared the two formulations. A crossover study in 9 patients did demonstrate significantly higher median posaconazole levels after patients transitioned from the oral suspension to DR; however, the sample size was small and limited to leukemic patients (8). Our data complement these

studies by demonstrating a clinical advantage of the DR tablet over the oral suspension in a real-world setting. Additionally, we not only demonstrated the ability to achieve posaconazole serum concentrations greater than 700 ng/ml as recommended when performing therapeutic drug monitoring for prophylaxis but also showed that patients administered the DR posaconazole tablet were more likely to achieve levels greater than 1,250 ng/ml, the cutoff suggested by current literature for monitoring posaconazole concentrations for IFI treatment (5).

Consistent with the prescribing information, which indicates a lack of drug interaction between DR posaconazole tablets and acid suppressants (12), acid suppression did not affect posaconazole levels in the DR tablet cohort. All patients in the DR tablet cohort were on an acid-suppressing medication, yet 90% achieved a therapeutic level. Previous studies have shown that the concomitant use of a proton pump inhibitor with posaconazole oral suspension significantly decreases its bioavailability (11, 14, 15). Our findings confirm that acid suppression does not significantly impact the absorption of the DR tablet formulation.

Patients who did not achieve an initial therapeutic posaconazole level did not differ significantly from the rest of their cohorts regarding dosing, diarrhea, mucositis, or GVHD. Given the small sample size, this may have been due to insufficient power to detect differences. However, other variables that were not collected, such as caloric intake or presence of fatty diet, may also have contributed to lower drug levels in these patients.

Our study has several limitations. The sample size was small, and the retrospective design hindered our ability to study more clinically relevant outcomes like prevention of IFI or treatment success; however, the number of patients in our study is larger than those in previous studies and raises the possibility of further prospective research. Another potential limitation is that all but 3 patients in the suspension cohort were treated in 2012 and 2013, while all patients in the DR cohort were treated in 2014, at which time physicians may have adjusted their recommendations to increase posaconazole absorption in patients. In addition, there were minor differences between the two cohorts, such as presence of IFI at initiation; this particular variable, however, is unlikely to affect posaconazole levels. Variables that might affect steady-state levels, including mucositis, diarrhea, and gastrointestinal GVHD, were very similar between the two groups. Our choice of 5 days from initiation as the threshold for a steady-state level is another limitation. Though this threshold is supported by one study (9), other studies have found 8 to 10 days from initiation to be the period when steady-state concentrations are achieved (16, 17), and median posaconazole level was significantly higher in our study when determined within 8 to 14 days of initiation than 5 to 7 days. However, our study also showed no significant trend of posaconazole levels over 5 to 14 days and no significant difference in timing of posaconazole level between our delayed-release cohort and oral-suspension cohort. In addition, timing of posaconazole level in relation to previous dose was not determined. However, based on pharmacy protocol, general practice at our institution is to order a trough level. Finally, we did not analyze toxicities between the cohorts. Given the high median drug levels in the DR cohort and the potential for increased toxicities, this would be an area for further research. One previous study used 2,500 ng/ml as an upper limit for a therapeutic level, although no supratherapeutic threshold has been clearly defined (13).

Despite these limitations, our study demonstrates that use of the DR tablet posaconazole formulation results in a higher likelihood of a therapeutic level than the oral suspension. More research is needed to further elucidate effects of the DR tablet posaconazole on clinical outcomes such as breakthrough infection, mortality, and toxicity.

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