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BRIEF REPORT

Evaluation of Posaconazole Serum Concentrations Achieved With Delayed-release Tablets and Oral Suspension in Patients Undergoing Intensive Chemotherapy for Acute Myeloid Leukemia and Myelodysplastic Syndrome

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Data on posaconazole serum levels of patients on prophylaxis with delayed-release tablets or oral suspension during intensive chemotherapy for acute myeloid leukemia and myelodysplastic syndrome are scarce. In this analysis, the proportion of patients with acute myeloid leukemia/myelodysplastic syndrome achieving posaconazole target concentrations with delayed-release tablets was higher than with oral suspension.

Keywords. acute myeloid leukemia; intensive chemotherapy; myelodysplastic syndrome; posaconazole prophylaxis.

In randomized controlled trials, posaconazole (PCZ) proved to be effective for prophylaxis of invasive aspergillosis in patients with remission-induction chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) [1] and in patients with graft-versus-host disease [2]. In cohort studies, PCZ prophylaxis was associated with a reduced risk for invasive aspergillosis after hematopoietic stem cell transplantation [3, 4].

Some evidence indicates that patients with high PCZ average plasma levels are less likely to experience breakthrough invasive fungal infection (bIFI) [5]. Current guidelines recommend therapeutic drug monitoring (TDM) when using PCZ oral suspension and to aim for PCZ levels >700 ng/mL for prophylaxis [6, 7]. Comparative data on PCZ steady-state trough levels between delayed-release (DR) tablets and oral suspension for patients with AML/MDS undergoing intensive induction chemotherapy, the most common indication for PCZ prophylaxis, are limited. In the sole study thus far, PCZ plasma levels at days 3, 8, and 15 were higher with DR tablets compared to oral suspension in Korean patients with AML/MDS undergoing intensive chemotherapy [8]. Other studies reported higher PCZ steady-state trough levels achieved with DR tablets than with oral suspension in patients undergoing hematopoietic stem cell transplantation [9] and in heterogeneous other study populations [10–15]. Data comparing differences in PCZ trough levels between the 2 oral formulations in patients with AML/MDS are vital for assessing the necessity of TDM when employing DR tablets for PCZ prophylaxis. Therefore, we assessed PCZ steady-state trough levels achieved with DR tablets and immediate release oral suspension in patients receiving PCZ prophylaxis during intensive chemotherapy for AML/MDS.

METHODS

We retrospectively identified adult patients (aged ≥18 years) with intensive first-line induction- or relapse chemotherapy for AML/MDS receiving PCZ prophylaxis and TDM from 1 June 2012 to 31 August 2018.

We analyzed PCZ prophylaxis courses of inpatients who had at least 2 PCZ trough level measurements available with the first measurement performed after 5 to 14 days after starting. This aligns with pharmacokinetic data indicating that PCZ steady-state concentrations are achieved within 5 days of starting prophylaxis [16]. The study was approved by the Ethics Committee of the Canton of Bern, Switzerland (project ID: 2021-01954).

Until July 2015, patients received PCZ prophylaxis in immediate release suspension form. Starting July 2015, patients received either DR tablets or immediate release oral suspension, with subsequent exclusive use of DR tablets. Our institution's protocol advised weekly monitoring of PCZ trough levels and did not allow concomitant proton-pump inhibitor treatment with PCZ oral suspension (but with DR tablets); however, concomitant treatment with ranitidine (H2 blocker) was allowed [17, 18]. The PCZ dosing regimen for DR tablets (300 mg twice per day as loading dose, followed by 300 mg once daily) and oral suspension (200 mg 3 times per day, administered with high-fat

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Table 1. Demographic Characteristics

Characteristic	Prophylaxis Course With Posaconazole Oral Suspension (n = 113)	Prophylaxis Course With Posaconazole DR Tablets (n = 104)	*P* Value
Sex			
Male, no. (%)	53 (46.9)	58 (55.8)	.192
Age [y], median (IQR)	58 (45–64)	57 (45–64)	.997
Body weight [kg], median (IQR)	68 (59–78)	73 (62–84)	.173
Disease			.019
AML, no. (%)	108 (95.6)	90 (86.5)	
MDS, no. (%)	5 (4.4)	14 (13.5)	
Neutropenia duration [d], median (IQR)	19 (14–25)	19 (14–26)	.891
Posaconazole prophylaxis duration [d], median (IQR)	20 (15–24)	23 (19–27)	<.001
Duration [d] to first PCZ steady-state measurement, median (IQR)	6 (6–7)	7 (6–8)	.911
Gastric acid-lowering agent use[a]			
PPI, no. (%)	12 (10.6)	100 (96.2)	<.001
H2 blocker (ranitidine), no. (%)	112 (99.1)	6 (5.8)	<.001
Neither PPI nor H2 blocker (ranitidine), no. (%)	1 (0.9)	0 (0.0)	.336
Antiepileptic drug use[b]			
Phenytoin, no. (%)	1 (0.9)	2 (1.9)	.513
Carbamazepine, no. (%)	0 (0.0)	0 (0.0)	NA
Other drugs potentially affecting PCZ levels[c]	0 (0.0)	0 (0.0)	NA

Three patients in the DR tablet group had sequentially at least 1 PPI dose and 1 H2 blocker (ranitidine) dose. Twelve patients in the oral suspension group had at least 1 PPI dose before they were switched to an H2 blocker.

Abbreviations: AML, acute myeloid leukemia; DR tablet, delayed-release tablet; H2 blocker, histamine-2 receptor blocker; IQR, interquartile range; MDS, myelodysplastic syndrome; NA, not applicable; PCZ, posaconazole; PPI, proton pump inhibitor.

[a]Defined as at least 1 concomitant PPI or H2 blocker dose in combination with posaconazole.

[b]Phenytoin may decrease the serum concentration of posaconazole. Carbamazepine may increase the serum concentration of posaconazole.

[c]Other drugs potentially affecting posaconazole levels: Ciclosporin, Rifamycins, Verapamil.

food or an acidic beverage [19, 20]) adhered to current guidelines [6]. If PCZ trough levels were <700 ng/mL or there was inability to tolerate oral medication, institutional guidelines suggested either PCZ dose escalation of the same compound or switching to intravenous antifungal drugs (amphotericin B deoxycholate or intravenous PCZ upon its availability in 2016; Supplementary data). Serum PCZ concentrations were measured at the Department of Clinical Chemistry, University Hospital of Bern, Switzerland (Supplementary data).

The primary outcome was the proportion of patients achieving PCZ target trough levels >700 ng/mL (DR tablets vs oral suspension) at the first steady-state measurement [5, 21]. Secondary endpoints included the comparison of average PCZ trough levels maintained during prophylaxis courses, the peak AST and ALT levels (safety endpoint), the proportion of patients with a PCZ dose escalation or switch to another prophylactic antifungal agent, and the description of bIFI (classified according to current European Organization for Research and Treatment of Cancer criteria [22]).

We employed descriptive statistics to summarize patient characteristics. We compared proportions using chi-squared tests or Fisher exact test, as applicable, whereas we analyzed continuous variables using the Wilcoxon rank-sum test. To compare the incidence rates of proven and probable bIFIs prophylaxis with DR tablets and oral suspension, we calculated the incidence rate ratio with a 95% confidence interval. Statistical significance was set at $P < .05$.

RESULTS

One-hundred and forty-one patients fulfilled the inclusion criteria (Supplementary Figure 1). These patients underwent 217 individual PCZ prophylaxis courses, 104 with DR tablets and 113 with oral suspension. Demographic information is provided in Table 1.

We measured 789 PCZ trough levels during the entire prophylaxis courses, 330 in patients receiving DR tablets and 459 in patients receiving oral suspension (Supplementary Figure 2). A higher proportion of patients receiving prophylaxis with DR tablets reached the target PCZ trough level at the initial steady-state measurement (DR tablets: 82.7%, 86/104; oral suspension: 61.9%, 70/113; $P = .001$). In a sensitivity analysis, these findings were consistent regardless of whether the initial steady-state PCZ measurement was conducted 5 to 14, 7 to 14, or 10 to 20 days after commencing prophylaxis (Supplementary Table 1). At the initial steady-state measurement, the median PCZ trough level was significantly higher in patients receiving prophylaxis with DR tablets (1220 ng/mL; interquartile range [IQR] 850-1855 ng/mL) compared to those receiving oral suspension (890 ng/mL; IQR 590-1170 ng/mL; $P < .001$) (Figure 1*A*). The average PCZ level maintained during individual prophylaxis cycles was higher with DR tablets (median average PCZ level DR tablets: 1030 ng/mL; IQR 788-1375 ng/mL. Median average PCZ level oral suspension: 703 ng/mL; IQR

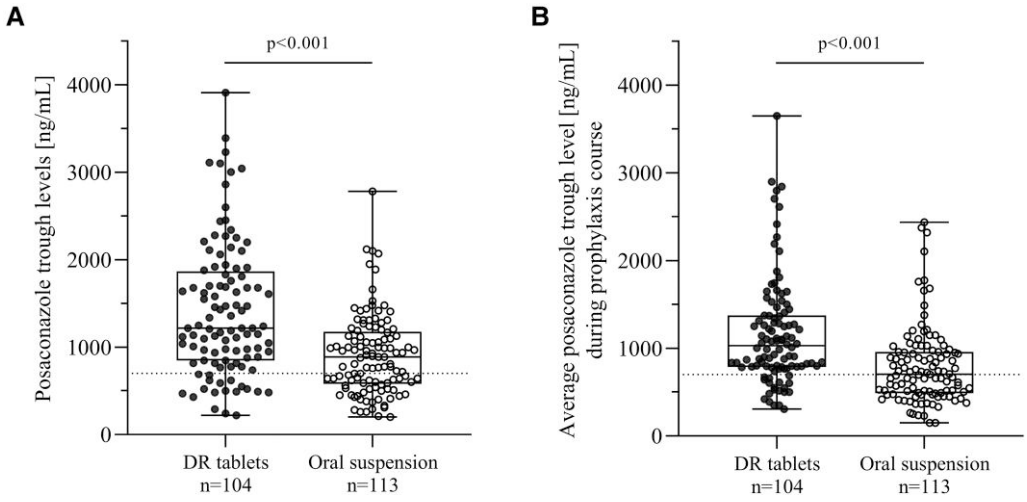

Figure 1. Posaconazole serum levels achieved by DR tablets and oral suspension. *A*, Posaconazole trough levels at first steady state measurement (5-14 d after initiating prophylaxis). *B*, Average posaconazole trough levels during the prophylaxis course. The dashed horizontal line indicates minimal posaconazole target level (>700 ng/mL). DR, delayed release.

490-960 ng/mL; $P < .001$) (Figure 1*B*). An average PCZ trough level exceeding 700 ng/mL was attained in 81.7% (85/104) and 50.4% (57/113) of cases with DR tablets and oral suspension, respectively ($P < .001$). These findings (higher levels during prophylaxis with DR tablets) were also confirmed when analyzing the proportion of PCZ measurements >700 ng/mL (DR tablets: 71.2%; oral suspension: 45.2%, $P < .001$).

AST and ALT levels were available for 98.6% (214/217) of PCZ prophylaxis courses. There was no difference in peak AST and ALT levels during PCZ prophylaxis with DR tablets (median peak AST: 41 U/L; IQR 26-72 U/L; median peak ALT: 79 U/L; IQR 45-140 U/L) compared with oral suspension (median peak AST: 41 U/L; IQR 25-70 U/L; $P = .519$; median peak ALT: 68 U/L; IQR 39-123 U/L; $P = .276$).

With both PCZ formulations, the frequency of dose escalation for maintaining PCZ target levels during prophylaxis was high (DR tablets: 34.6%, 36/104; oral suspension: 34.5%, 39/113; $P = .987$). Physicians switched more often to another (non-PCZ-based) prophylactic antifungal compound when patients received oral suspension (DR tablets: 0.96%, 1/104 vs oral suspension: 25.6%, 31/113; $P < .001$).

Supplementary Table 2 outlines the characteristics of proven and probable bIFI. Incidence rates of both proven and probable bIFI were comparable between prophylaxis courses with DR tablets (2.42 cases per 1000 prophylaxis days) and oral suspension (2.17 cases per 1000 prophylaxis days), with an incidence rate ratio of 1.12 (95% confidence interval, 0.28-4.62; $P = .455$).

The majority of patients (72.7%, 8/11) diagnosed with proven and probable bIFI exhibited PCZ levels ≤ 700 ng/mL at their last measurement before bIFI diagnosis. PCZ prophylaxis courses complicated by proven and probable bIFI were associated with a longer duration of severe neutropenia (median: 35 days; IQR 28-42) compared to those without bIFI (median: 19 days; IQR 13-25; $P < .001$).

DISCUSSION

In this retrospective cohort of patients with AML/MDS undergoing intensive chemotherapy, PCZ prophylaxis with DR tablets resulted in a higher proportion of patients initially reaching the target trough level (>700 ng/mL) than oral suspension. Average PCZ trough levels were consistently higher with DR tablets. The rate of PCZ dose escalation during prophylactic courses was notably high at approximately 30%, regardless of the formulation used. The majority of patients diagnosed with proven and probable bIFI had PCZ trough levels below 700 ng/mL before bIFI diagnosis.

A previous study also compared PCZ steady-state trough levels of DR tablets and oral suspension in patients with AML/MDS undergoing intensive chemotherapy [8]. Consistent with our findings, DR tablets yielded higher steady-state PCZ trough levels compared to oral suspension. The percentage of patients achieving PCZ levels >700 ng/mL at days 8 and 15 was notably greater in the DR tablet group [8]. Similar findings were reported in previous cohort studies involving heterogeneous patient populations [9–15].

The high proportion of patients achieving average PCZ trough levels >700 ng/mL (DR tablets 96.2%; oral suspension 85.0%) in our cohort must be interpreted in the context of the particular conditions at our cancer center. All patients on PCZ prophylaxis undergo routine TDM and the laboratory performs measurements twice weekly with same-day result

reporting. If PCZ steady-state levels are ≤700 ng/mL, the PCZ dose will be increased or the patient is switched to an intravenous antifungal agent. The high proportion of PCZ prophylaxis courses with dose escalation (~30% for both formulations) reflects this institutional practice. Therefore, our data do not support omitting routine TDM in patients on PCZ prophylaxis with DR tablets.

One strength of our study is its focus on patients undergoing intensive chemotherapy for AML/MDS, the primary indication for PCZ prophylaxis. Unlike many prior studies with heterogeneous populations, our findings are directly applicable to this specific target group. Despite this narrower focus, we achieved a respectable sample size (217 PCZ prophylaxis cycles). An innovative aspect of our study is the repeated PCZ trough level measurements, offering insights into average levels during prophylaxis and the necessity for dose adjustments to attain target levels. Our retrospective study design is limited by the lack of randomization in assigning patients to receive PCZ DR tablets or oral suspension. Because of the study design (retrospective study), it was not possible to provide reliable information on diarrhea or mucositis, both conditions that may affect PCZ absorption. A minority of patients on prophylaxis with oral suspension (12/113) received concomitant proton-pump inhibitor therapy, which may result in lower PCZ levels [17]. Moreover, bIFIs were infrequent, leading to a sample size that was insufficient to comprehensively evaluate differences in incidence between the 2 PCZ formulations.

In summary, the proportion of patients achieving PCZ target serum concentrations with DR tablets was higher than with oral suspension. For both PCZ formulations, dose escalation was frequently needed to achieve desired serum concentrations; therefore, TDM should also be considered when administering PCZ prophylaxis in a DR tablet formulation for patients with intensive chemotherapy for AML/MDS.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Patient consent statement. The study was approved by the Ethics Committee of the Canton of Bern, Switzerland (project ID: 2021-01954). All patients provided written informed consent for further use of health related data for research purpose.

Potential conflicts of interest. All authors: No reported conflicts.

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