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Original Article

Serum posaconazole levels among haematological cancer patients taking extended release tablets is affected by body weight and diarrhoea: single centre retrospective analysis

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Summary

The posaconazole extended release tablet formulation was developed to improve bioavailability relative to the oral suspension. Therapeutic drug monitoring has been used to optimise posaconazole dosing to achieve a target trough level ≥0.7 μg ml^{-1}. We retrospectively evaluated 28 patients with haematological malignancies who received posaconazole tablets for antifungal prophylaxis. Posaconazole serum trough levels were obtained 5 days after initiation of therapy. Mean trough level was 1.19 ± 0.63 μg ml^{-1}, and 71% achieved a trough level ≥0.7 μg ml^{-1}. Diarrhoea was associated with lower mean trough levels (0.65 ± 0.08 μg ml^{-1} vs. 1.31 ± 0.13 μg ml^{-1}), $P = 0.002$. Mean trough levels were lower in patients ≥90 kg (0.74 ± 0.09 μg ml^{-1}) vs. <90 kg (1.32 ± 0.14 μg ml^{-1}), $P = 0.002$ and in patients with body mass index (BMI) ≥30 (0.89 ± 0.13 μg ml^{-1}) vs. BMI <30 (1.29 ± 0.14 μg ml^{-1}), $P = 0.05$. Posaconazole delayed release tablets attain appropriate trough levels in most patients, but patients with a higher weight and those experiencing diarrhoea are more likely to have lower levels.

Key words: Posaconazole tablets, therapeutic drug monitoring, antifungals.

Introduction

Patients with acute myeloid leukaemia (AML) and patients undergoing haematopoietic cell transplantation (HCT) are at high risk of developing invasive fungal infections.[1,2] Early antifungal treatment and prevention are critical to improve survival of these patients. Posaconazole is an antifungal triazole used for prophylaxis in patients with AML and HCT recipients.[3,4] Use of posaconazole prophylaxis is one of the few interventions that has improved overall survival in AML.[3] Initially, this agent was available only as a suspension that had rate-limiting absorption, was hampered by inter- and intra-patient pharmacokinetic variability, with a potential for suboptimal trough levels and breakthrough fungal infections.[5] Furthermore, posaconazole suspension had to be administered with food, which was another practical problem in a patient population with frequent mucositis, nausea and vomiting due to chemotherapy. Thus, therapeutic drug monitoring of posaconazole has become a valuable clinical tool to ensure that optimal drug levels are achieved and efficacy is enhanced.

The Food and Drug Administration has recently approved a delayed release posaconazole tablet formulation that is reported to improve oral bioavailability. The pharmacokinetics and safety of the new formulation is based on healthy volunteer studies.[6–8] This

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report describes our experience using the delayed release posaconazole tablet for prophylaxis in high-risk patients, with a focus on clinical parameters that may impact serum posaconazole levels, and that could be used as an aid to individualise dosing of this new formulation.

Material and methods

This is a retrospective chart review study of patients undergoing chemotherapy for AML and HCT recipients who received delayed release posaconazole tablets for prophylaxis from 1 February 2014 through 15 May 2014. Patients were eligible for the study if they received posaconazole tablets at the recommended dose of 300 mg twice daily on day 1 followed by 300 mg daily, and posaconazole steady state serum trough levels were obtained on day 5. Patients were excluded if they were already receiving posaconazole or were being treated with a different dose of posaconazole than that recommended by the package insert. This study was approved by the University of Michigan Healthcare System Institutional Review Board.

Posaconazole serum trough levels were measured using high-performance liquid chromatography assay-tandem mass spectrometry (performed at Mayo Clinic Department of Laboratory Medicine and Pathology, Rochester, MN). Therapeutic posaconazole serum trough concentration was defined as ≥ 0.7 μg ml^{-1} as previously suggested for prophylactic antifungal efficacy.[9,10] Relevant demographics and patient characteristics, including body mass index (BMI) and actual body weight in kilograms, were obtained through chart review. Clinical data, including diarrhoea, oral intake, and concomitant use of proton-pump inhibitors (PPI) or histamine-2 receptor antagonists (H_2RAs) were recorded.

Diarrhoea was defined as frequent and watery bowel movement based on the Common Terminology Criteria for Adverse Events definitions (CTCAE version 4.03: any increase of ≥4 stools per day over baseline, faecal incontinence, or moderate to severe increase in ostomy output compared to baseline).[11]

All statistical analyses were performed using GraphPad Software (San Diego, CA). Statistical differences between groups were determined using a Student's *t*-test with Welch's correction and a one-way analysis of variance (ANOVA) with a Turkey's multiple comparison test performed between groups for additional comparisons. Pearson correlation coefficient was calculated to assess the relationship between BMI and posaconazole serum trough levels and between actual body weight and posaconazole serum trough levels. Quantitative variables were reported as the number (percentage) and continuous variables as the mean ±standard error of the mean (SEM). A value of $P < 0.05$ was considered significant.

Results

A total of 28 patients (22 receiving chemotherapy for AML and 6 HCT recipients) received the recommended dose of posaconazole and had a posaconazole serum trough level drawn on day 5 (Table 1). The day 5 mean serum trough level was 1.19 ± 0.63 μg ml^{-1} (range: 0.36–2.50 μg ml^{-1}). Seventy-one percent of the patients achieved the target level of ≥ 0.7 μg ml^{-1}.

The effect of concomitant use of proton-pump inhibitors/histamine-2 receptor antagonists, diarrhoea, oral intake and weight on posaconazole serum trough levels at day 5 are reported in Table 2. Twenty-three of 28 patients were treated with either a PPI or H_2RAs. Mean trough levels among patients receiving these agents was 1.11 ± 0.12 μg ml^{-1} vs. mean trough levels of 1.62 ± 0.32 μg ml^{-1} among patients not receiving either of these agents ($P = 0.19$).

Five patients who had diarrhoea documented during the 5 days prior to obtaining the serum trough concentration had mean posaconazole trough level of 0.65 ± 0.08 μg ml^{-1} compared with a mean of 1.31 ± 0.13 μg ml^{-1} in patients without diarrhoea ($P = 0.002$). Only 2 of 5 patients (40%) with diarrhoea achieved posaconazole trough concentrations ≥ 0.7 μg ml^{-1} compared with 20 of 23 patients (86%) who did not have diarrhoea.

Three of twenty-eight patients were fasting during treatment with posaconazole extended release tablets.

Table 1 Patient demographics.

Demographic characteristics	Patient data
Age, year, mean (range)	53 (19–77)
Male	16 (57%)
Race/ethnicity	
Caucasian	23 (82%)
African American	2 (7%)
Hispanic	2 (7%)
Unknown	1 (4%)
Actual body weight, kg (mean, range)	79.8 (54.7–122.3)
<90 kg, *n* (%)	22 (78.5%)
≥90 kg, *n* (%)	6 (21.5%)
Body mass index[1], kg/m^2 (mean, range)	27 (20.4–36.9)
<30, *n* (%)	21 (75%)
≥30, *n* (%)	7 (25%)

[1]There were no patients with BMI below 20.

Table 2 Effect of oral intake, concomitant use of proton-pump inhibitors/histamine-2 receptor antagonists, diarrhoea, and weight on posaconazole serum trough levels at day 5.

Risk factor		Patients, *n* (%)	Posaconazole trough level (mean ±SD)	*P* value
Oral intake	Yes	25 (89%)	1.25 ± 0.13 μg ml^{-1}	–
	No	3 (11%)[1]	0.71 ± 0.08 μg ml^{-1}	
Concomitant use of PPI/H2RA[2]	Yes	23 (82%)	1.11 ± 0.12 μg ml^{-1}	NS
	No	5 (18%)[3]	1.62 ± 0.32 μg ml^{-1}	
Diarrhoea	Yes	5 (82%)	0.65 ± 0.08 μg ml^{-1}	0.002
	No	23 (18%)	1.31 ± 0.13 μg ml^{-1}	
BMI[4]	<30	21 (75%)	1.29 ± 0.14 μg ml^{-1}	0.05
	≥30	7 (25%)	0.89 ± 0.13 μg ml^{-1}	
Actual body weight (kg)[4]	<90	22 (78%)	1.32 ± 0.14 μg ml^{-1}	0.002
	≥90	6 (22%)	0.74 ± 0.09 μg ml^{-1}	

[1]All three patients had diarrhoea, no further analysis was possible after excluding these patients.

[2]PPI/H2RA, proton-pump inhibitors/histamine-2 receptor antagonists.

[3]Only one of five patients who did not receive PPI/H2RA had diarrhoea, posaconazole trough level for that patient was 0.84 μg ml^{-1}.

[4]After excluding patients with diarrhoea, patient weight and BMI affected posaconazole levels significantly (see Fig. 1b).

Posaconazole serum trough levels for these patients were 0.72, 0.84 and 0.57 μg ml^{-1}; the last two patients also had diarrhoea. The remaining 25 patients were not fasting and received posaconazole without regard to food, achieving mean posaconazole serum trough levels of 1.25 ± 0.13 μg ml^{-1}. Three of these 25 patients also had diarrhoea; posaconazole trough levels were 0.4, 0.68 and 0.76 μg ml^{-1} respectively.

We evaluated the effect of weight on posaconazole trough concentration levels of all 28 patients included in the study. We observed that mean posaconazole trough concentrations were lower in patients who weighed ≥90 kg (0.74 ± 0.09 μg ml^{-1}) compared with those who weighed <90 kg (1.32 ± 0.14 μg ml^{-1}) ($P = 0.002$). Similarly, mean posaconazole trough levels were lower in patients with BMI ≥ 30 (0.89 ±0.13 μg ml^{-1}) compared with BMI < 30 (1.29 ±0.14 μg ml^{-1}), $P = 0.05$ (Fig. 1a).

Because of the effect of diarrhoea on posaconazole trough levels noted above, we conducted a separate analysis of the effect of weight on posaconazole trough levels in the 23 patients who did not have diarrhoea. Patients who weighed ≥90 kg had lower posaconazole trough levels (mean 0.75 ± 0.14 μg ml^{-1}) compared

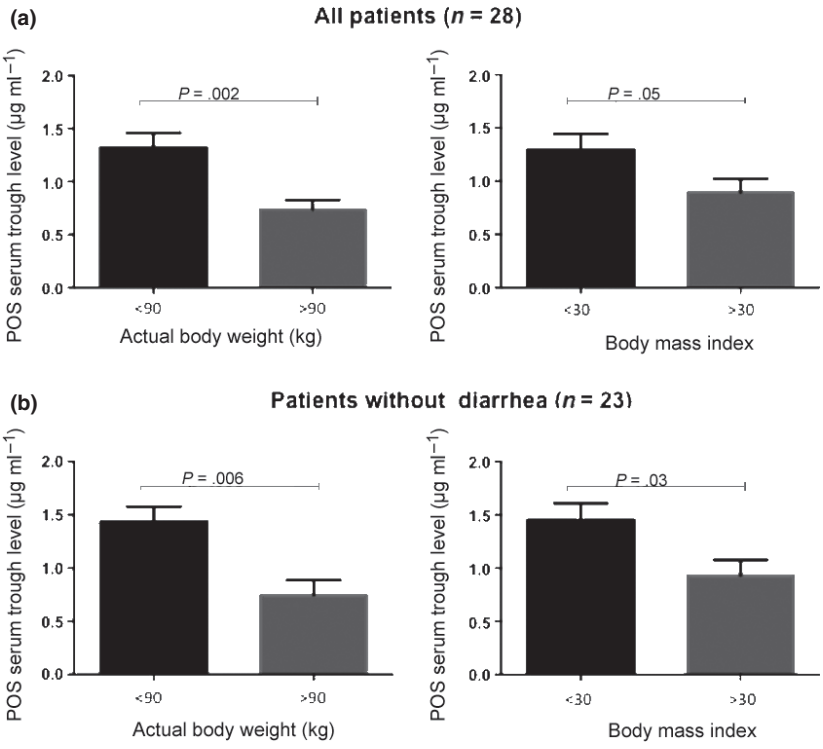

Figure 1 Effect of body mass index and actual body weight on posaconazole serum trough level. (a) Distribution of mean posaconazole serum trough levels in all 28 patients based on actual body weight (<90 vs. ≥90 kg) and body mass index (<30 vs. ≥30). (b) Distribution of mean posaconazole serum trough levels when five patients who had diarrhoea were excluded from the analysis. Patients are divided based on actual body weight (<90 vs. ≥90 kg) and body mass index (<30 vs. ≥30).

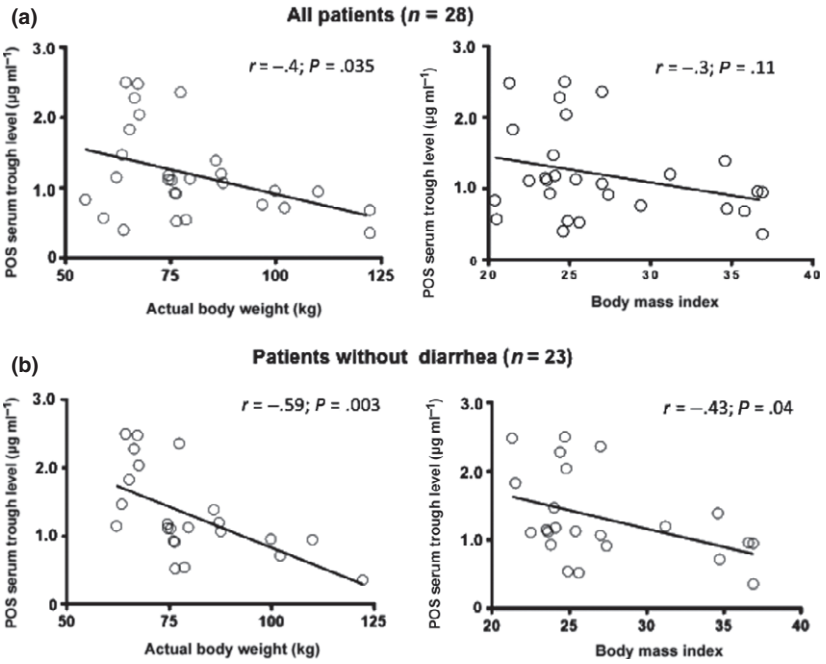

Figure 2 Correlation between body mass index/actual body weight and posaconazole serum trough level. (a) Distribution of actual body weight and body mass index in all 28 patients and its correlation with posaconazole serum trough levels. (b) Distribution of actual body weight and body mass index and the correlation with posaconazole serum trough levels, after excluding the five patients who had diarrhoea.

with those who weighed <90 kg (1.43 ± 0.14 μg ml^{-1}) ($P = 0.006$). In patients without diarrhoea, mean posaconazole trough levels were lower in patients with BMI ≥30 (0.93 ± 0.15 μg ml^{-1}) compared with BMI <30 (1.45 ± 0.16 μg ml^{-1}), ($P = 0.03$) (Fig. 1b).

Scatterplots presented in Fig. 2 summarise the distribution of body weight and BMI in the patient population and the relationship with posaconazole serum trough levels. Patients who had higher body weight (≥90 kg) and higher BMI (≥30) had lower posaconazole serum trough levels (correlation coefficient $r = -0.4$, $P = 0.035$ and $r = -0.3$, $P = 0.15$ respectively) (Fig. 2a). This correlation achieved greater significance when patients with diarrhoea were excluded from the analysis (correlation coefficient $r = -0.59$, $P = 0.003$ and $r = -0.43$, $P = 0.04$ respectively) (Fig. 2b).

Discussion

This report describes our experience using delayed release posaconazole tablets for prophylaxis in high-risk patients. Our findings suggest that this formulation overcomes some of the expected variation in serum trough levels that has been seen with posaconazole solution.

Therapeutic drug monitoring of serum concentrations is a surrogate for assessing patient exposure and drug efficacy in the clinical setting.[9] Although data are conflicting, in clinical practice a target posaconazole trough concentration of ≥0.7 μg ml^{-1} is used for the prevention of invasive fungal infections.[5,10,12–14] In our study, the majority (>70%) of patients attained serum trough concentrations ≥0.7 μg ml^{-1}. However, patients with BMI ≥30 or actual body weight ≥90 kg were more likely to have suboptimal levels.

A cutoff of below and above 90 kg actual body weight was chosen in this study as it was our anecdotal clinical observation that patients above this threshold attained lower posaconazole serum concentrations. Indeed, it was this observation that led us to conduct the present study. Similarly, we used BMI cutoff of below and above 30 based on the World Health Organization's definition for obesity.[15] Pathophysiological changes seen in patients with higher BMI, such as changes in blood volume, cardiac output, volume of distribution, protein binding, and hepatic metabolism, may alter the pharmacokinetics of posaconazole.[16,17] Furthermore, we speculate that as posaconazole is a lipophilic antifungal agent, it may distribute into the excess adipose tissue of obese patients leaving less drug available in the serum.[18] Lastly, posaconazole is metabolised via glucuronidation, which is increased in obesity, potentially leading to increased metabolism, elimination, and decreased exposure of posaconazole.[16] Interestingly, in our study, the coefficient of correlation was higher for the body weight than the BMI. As the BMI is a function of body weight and height, it is possible that patient body weight is the attributable variable for the trough concentration. This may be a reflection of the limitations of BMI. Indeed, BMI is

truly a measure of excess weight, rather than excess adiposity. Age, sex, muscle mass can all skew the accuracy of BMI. Whether total body weight, BMI or both are relevant covariates for posaconazole serum levels needs further investigation.

Patients with diarrhoea manifested suboptimal trough concentrations. We speculate that lower trough levels observed in these patients could be due to gastrointestinal disruption and an increase in gastric emptying, both resulting in less absorption.

Our study has several limitations. We studied a small number of patients from a single centre. Ideally tissue and not serum concentrations would have given a better indication of posaconazole pharmacokinetics.[19] From this study, it is not known whether obese patients attain high tissue concentrations despite lower serum levels.

Clinicians should consider therapeutic drug monitoring when using posaconazole, particularly in patients with higher weight and BMI and those with diarrhoea. Further studies are necessary to determine the optimal dosing regimen in these patients.

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Conflict of interests

Dr. Daniel Couriel serves as a member of the Medical Advisory Board for Merck, Sharp and Dohme Corporation. He also receives research funding from Therakos, Inc. All other authors have no conflict of interest to report.

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