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Early Therapeutic Drug Monitoring of Posaconazole Oral Suspension in Patients with Hematologic Malignancies

혈액암 환자에서 포사코나졸 현탁액의 조기 치료약물농도모니터링

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Abstract

Early Therapeutic Drug Monitoring of Posaconazole Oral Suspension in Patients with Hematologic Malignancies

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Background:

Therapeutic drug monitoring (TDM) of posaconazole is usually performed one week after starting the drug because of its long half-life. However, previous studies showed that measuring the posaconazole plasma concentration (PPC) on day 3 is effective for predicting steady-state levels. The purpose of this study was to evaluate the relevance of early TDM (day 3) of posaconazole for achieving an optimal PPC.

Methods:

Patients with acute myeloid leukemia or myelodysplastic syndromes who received posaconazole oral suspension for fungal prophylaxis during chemotherapy were included in this study. For early TDM group, PPCs were measured on day 3, and the frequency of posaconazole administration was increased when PPC on day 3 was <400ng/mL. For control group, no dose adjustment was performed on day 3. PPCs on day 3 and day 8 were compared between the two groups. The cut-off value for optimal PPC on day 8 was defined as >500ng/mL.

Results:

A total of 107 patients were included in the control group, and 41 patients were included in the early TDM group. On day 3, PPC was <400ng/mL in 21 (20%) of 107 patients in control group, whereas 4 (10%) of 41 patients in early TDM group. On day 8, PPC was optimal in 87/107 (81%) in the control patients, whereas 36/41 (88%) in the early TDM group. In subgroup analysis for the patients whose PPC was <400ng/mL on day3, PPCs on day 8 was optimal in 6/21 (29%) in the control group, whereas 3/4 (75%) in the early TDM group.

Conclusions:

Posaconazole TDM on day 3 may be helpful in achieving optimal plasma concentration in haematological patients receiving chemotherapy.

Key words: posaconazole, therapeutic drug monitoring, early TDM, fungal prophylaxis

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Contents

List of table and figures

Introduction

Posaconazole is approved as a prophylactic antifungal agent for chemotherapy in patients with hematologic malignancies and has proven to be more effective than other antifungal agents.[1-3] It was first approved as an oral suspension formulation in 2006,[4] then tablets and an intravenous formulation were approved in 2013 and 2014, respectively. These formulations have proved to be more effective in fungal prophylaxis without increasing side effects.[5] However, posaconazole oral suspension is still an important alternative to patients with swallowing difficulties in circumstances where the intravenous formulation is not available.

The bioavailability of posaconazole oral suspension is affected by various conditions.[6,7] Risk factors for low posaconazole plasma concentration (PPC) include lack of enteral nutrition, vomiting, diarrhea, acid-lowering agent, concomitant chemotherapy, and graft-versus-host disease.[8,9] Moreover, posaconazole exposure is insufficient in more than 40% of patients at risk of invasive fungal infections (IFI),[8] and there is a substantial interpatient variability in posaconazole exposure of between 71% and 86%.[10] Since it is difficult to predict the bioavailability of posaconazole oral suspension in patients with hematologic malignancies who have poor oral intake and mucositis while undergoing chemotherapy, various dosing

strategies were studied. We showed that increasing the frequency of posaconazole administration to 200 mg four times daily (800 mg/day) can improve PPC.[11] However, several studies have shown that administration of posaconazole oral suspension above 800 mg/day does not increase PPC because of saturation of absorption.[12,13]

Also, because of the unpredictable bioavailability and interpatient variability of posaconazole, some studies have reported the usefulness of posaconazole therapeutic drug monitoring (TDM).[10,14] It can play an important role in achieving target PPC, preventing IFI and improving clinical outcome to therapy in real-world studies.[8,9,15] Traditionally, posaconazole TDM is usually performed one week after starting the drug because it has a long half-life of nearly 35 hours.[16] However, previous studies showed that measuring PPC on day 2 or day 3 is effective for predicting steady-state levels.[12,17,18] There have been several studies suggesting early TDM (day 2) based on pharmacokinetic data,[19,20] but the level of evidence was low because there was no study that showed the usefulness of early TDM (day 3) in real-world clinical settings. The purpose of this study was to evaluate the relevance of early TDM of posaconazole in achieving an optimal PPC in patients with hematologic malignancies receiving posaconazole oral suspension as a prophylactic antifungal agent.

Materials and Methods

This study was conducted at two university-affiliated hospitals in South Korea (Seoul National University Hospital, Seoul, South Korea and Seoul National University Bundang Hospital, Seongnam, South Korea) from September 2014 to August 2016. Patients were aged ≥18 years old and were undergoing chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) and received posaconazole as a prophylactic antifungal agent. Patients were excluded if they refused to participate or if either the day 3 or day 8 PPC was not obtained for any reason. Posaconazole plasma concentrations were measured on day 3 and day 8 by liquid chromatography-tandem mass spectrometry.[21]

During the period from September 2014 to December 2015 (Control group), no dose adjustment was performed on day 3. However, from Jan 2016 to Aug 2016 (early TDM group), the frequency of posaconazole administration was increased to 200 mg four times daily if the PPC on day 3 was <400 ng/mL. After this intervention, we measured the PPC on day 8. The cut-off value on day 3 was 400 ng/mL because it was the most predictable value that optimal PPC could be reached on day 8 based on our previous data. Also, we set the optimal PPC to 500 ng/mL based on the MIC_{90} value for *Aspergillus* spp.[22]

To maintain therapeutic drug levels, posaconazole was administered with a meal or nutritional supplement. Acid-lowering agents including proton pump inhibitors (PPIs) and H_2 blockers were allowed if the attending physicians considered it essential for patient care. Daily dietary information including fat content was monitored prospectively. Informed written consent was obtained from every patient. This study was approved by the Institutional Review Boards of both study hospitals.

The study was designed with 80% power at a significance level of 0.05 to detect a risk ratio of 2 or more, assuming a proportion of suboptimal PPC on day 8 of 20%. The design required 219 cases in both groups and a total of approximately 438 cases. Univariate analysis was performed to test for differences between groups. We used Student's t-test and the chi-square test or Fisher's exact test, Mann-Whitney test depending on the type of variable. p Values <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp. Armonk, NY, USA).

Results

From September 2014 to December 2015, 107 patients were enrolled (Control group) and from January 2016 to August 2016, 41 patients were enrolled (early TDM group) (Figure 1). In the control group, the average age was 52 (range 19–77) years, 57.9% of cases were male (62/107), and 91.6% of cases had AML (98/107) (Table 1). The average PPC on day 3 and day 8 was 767.2 and 1025.6 ng/mL, respectively. In the early TDM group, the average age was 56 (range 28–80) years, 46.3% of cases were male (19/41), and 85.4% of cases had AML (35/41). The average PPC on day 3 and day 8 was 789.7 and 1033.6 ng/mL, respectively. There were no significant differences between the two groups except for age (Table 1).

In the control group, PPC was <400 ng/mL on day 3 in 20% (21/107) of the patients. Among these 21 patients, PPC was suboptimal on day 8 in 71% (15/21). In the early TDM group, PPC was <400 ng/mL on day 3 in 10% (4/41) (Table 2). Among these four patients, the frequency of posaconazole administration was increased. After the intervention, PPC was suboptimal on day 8 in one patient (25%) whose PPC was 181 ng/mL on day 3. This patient had no gastrointestinal problems such as mucositis or diarrhea and did not take H2 blockers or proton-pump inhibitors, but the patient's PPC was still suboptimal (327 ng/mL) on day 8. In both groups,

six patients had PPC <200 ng/mL on day 3 and 83% (5/6) of these patients failed to reach the optimal PPC on day 8.

Considering the patients with low PPC on day 3 in both groups, mean PPC was 388.2 and 717.3 ng/mL, respectively (Figure 2). Overall, the PPC on day 8 was suboptimal in 19% (20/107) of the patients in the control group and 12% (5/41) of the patients in the early TDM group ($p = 0.345$). In both groups, 104 patients had a PPC of ≥500 ng/mL on day 3, but 7% (7/104) of these patients had a suboptimal level on day 8. During the study period, there were no proven IFI, four provable IFI (two in the control group and two in the early TDM group), and one patient in the control group died due to IFI.

Table 1. Characteristics of the study subjects

Characteristics	**Control group (N = 107)**	**Early TDM group (N = 41)**	**p**
Mean age ± SD, years	51.6 ± 13.4	56.4 ± 12.4	0.049
Male sex, n (%)	62 (57.9)	19 (46.3)	0.204
Mean height ± SD, cm	164.4 ± 8.6	163.4 ± 9.1	0.500
Mean weight ± SD, kg	64.2 ± 11.7	63.4 ± 11.6	0.699
Hematologic disease, n (%)			0.262
AML	98 (91.6)	35 (85.4)	
MDS	9 (8.4)	6 (14.6)	
Calorie intake (kcal/day)	1444.5 ± 559.3	1331.1 ± 459.5	0.188
Fat content (g/day)	41.4 ± 15.5	38.5 ± 13.0	0.285
Acid lowering agents, n (%)	17 (15.9)	6 (14.6)	0.851
H2 blocker, n (%)	12 (11.2)	5 (12.2)	0.867
PPIs, n (%)	5 (4.7)	1 (2.4)	0.537
Mucositis ≥grade 2, n (%)	6 (5.6)	3 (7.3)	0.708
Diarrhea ≥grade 2, n (%)	9 (8.4)	3 (7.3)	1.000

AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; SD = standard deviation; PPI = proton pump inhibitors.

Table 2. Change in posaconazole plasma concentration (PPC) in both groups.

	Control group (N = 107)	**Early TDM group (N = 41)**	**p**
Mean day 3 PPC ± SD, ng/mL	767.2 ± 421.9	789.7 ± 409.5	0.769
Mean day 8 PPC ± SD, ng/mL	1025.6 ± 655.3	1033.6 ± 604.7	0.946
PPC <400 ng/mL on day 3, n (%)	21 (19.6)	4 (9.8)	0.220
PPC <500 ng/mL on day 8, n (%)	20 (18.7)	5 (12.2)	0.345

SD = standard deviation.

Figure 1. Study flow diagram. (A) control group, (B) early TDM group.

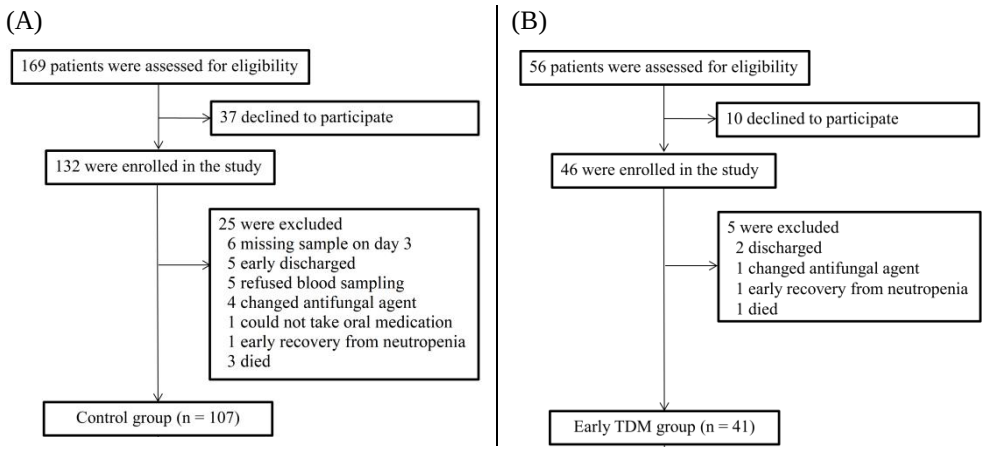
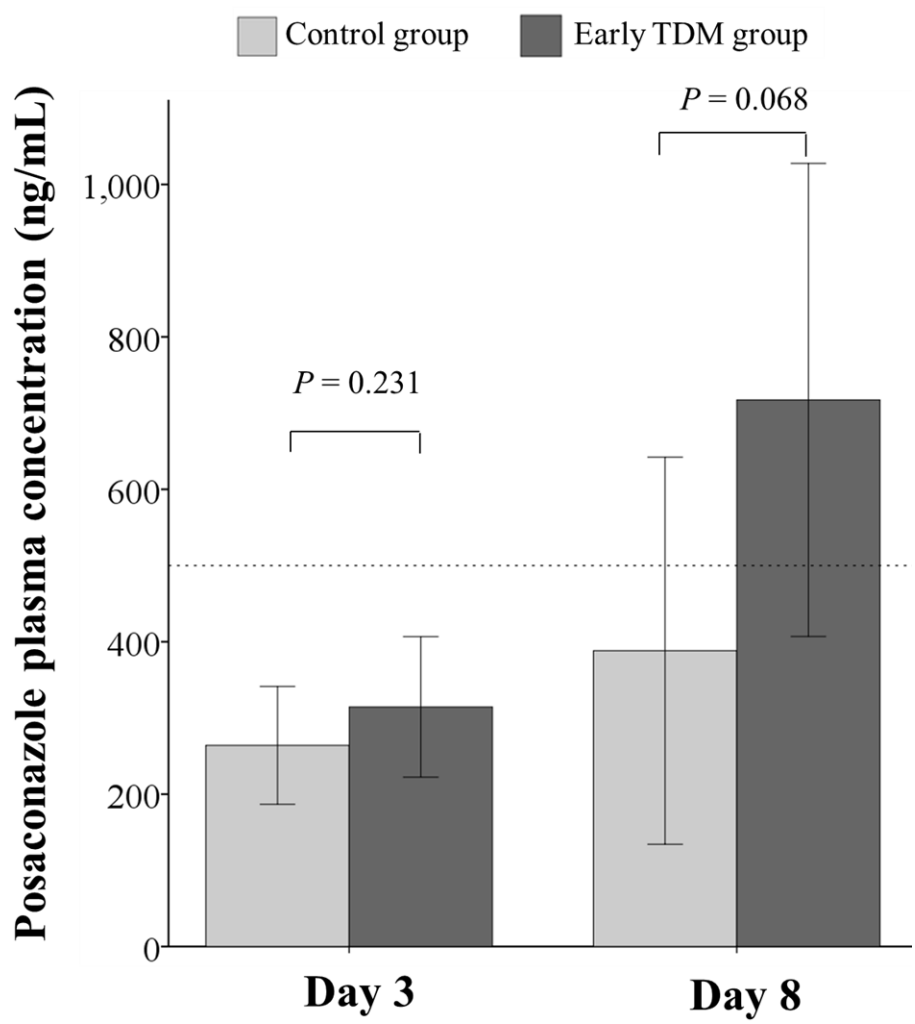


Figure 2. Mean posaconazole plasma concentration (PPC) in patients with low PPC (<400 ng/mL) on day 3 in both groups. The dotted line represents the cut-off value for optimal PPC (500 ng/mL) on day 8. Each error bar represents one standard deviation.



Discussion

Previous studies suggested that day 2 or day 3 PPC can predict steady-state levels of posaconazole.[12,17,18] However, the evidence level for early TDM was still low[23] because there was no previous study about early TDM in a real-world setting. Therefore, we studied the usefulness of early TDM of posaconazole in patients with hematologic malignancies. When analyzing the patients who had PPC <400 ng/mL on day 3, the proportion with a suboptimal PPC on day 8 was 71% in the control group and 25% in the early TDM group. This finding suggests that early TDM for posaconazole helps to identify patients who need increased doses to achieve optimal drug levels. However, of the patients whose PPC were ≥500 ng/mL on day 3, about 7% of the patients did not reach the optimal level on day 8. Therefore, even when the PPC was ≥500 ng/mL on day 3, the TDM should not be omitted on day 8.

Among both groups, there were six patients with PPC <200 ng/mL on day 3. Of these patients, 83% did not reach the optimal PPC on day 8. In one of these patients, posaconazole administration frequency was increased from three times daily to four times daily, but the PPC was suboptimal. In our previous study, low PPC on day 8 was a risk factor for a suboptimal level on day 15 despite increasing the administration frequency.[11] There

were three patients with levels of <200 ng/mL on day 8, and all of them had suboptimal levels on day 15 despite increasing the administration frequency.[9] These findings suggest that if a patient has a PPC <200 ng/mL, it is difficult to reach the optimal PPC with a posaconazole oral suspension. In these patients, genetic factors such as *UGT1A4* polymorphisms can affect the posaconazole level,[24] so antifungal agents other than posaconazole oral suspension should be considered. Early TDM on day 3 for posaconazole may help detect these poor absorbers earlier, which can facilitate these patients receiving a more appropriate antifungal agent sooner.

The only posaconazole-associated adverse event was a case of grade 1 diarrhea that occurred in control group. The mean PPC of the early TDM group was higher than that of the control group, but it was not associated with increasing adverse events. Other studies have also shown that increasing the administration frequency of posaconazole oral suspension is not associated with increasing adverse events.[5,25]

This study has a few limitations. First, the study design required a total of 438 cases at the time of the initiation of the study. However, the sample size was small, and statistically significant differences between groups in achieving optimal PCC could not be shown due to the small number of cases. Also, it was not enough to analyze the correlation with the incidence of breakthrough IFI. Second, this study was not randomized.

There might be confounding factors when comparing the control and early TDM groups, although there were no significant differences between the two groups except for age. Third, we set the target PPC to ≥500 ng/mL. Based on pharmacokinetic studies, the target PPC for fungal prophylaxis has been proposed between 500 and 700 ng/mL and the target PPC of ≥500 ng/mL was supported in several studies.[26] However, the target PPC of ≥700 ng/mL has now been preferable to minimize the risk of breakthrough IFI.[10] Despite these limitations, the present study is meaningful because it is the first prospective, proof-of-concept study for early TDM for posaconazole in actual clinical practice, and it showed that early TDM for posaconazole could possibly help to modify the administration frequency of posaconazole or to switch the patient to another antifungal agent sooner. In addition, although posaconazole tablet with improved bioavailability has been used, it can sometimes be a problem with suboptimal PPC when applied to hematologic patients with mucosal damage. Therefore, the results of this study may be helpful in other formulations as well as posaconazole oral suspension.

Conclusion

Early TDM on day 3 of posaconazole oral suspension may help more patients with hematologic malignancies achieve optimal posaconazole levels on day 8 and provide early screening for poor absorbers.

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국문 초록

배경

포사코나졸은 긴 반감기를 가지고 있기 때문에 포사코나졸 투약 시작 후 8일 째에 치료약물모니터링(therapeutic drug monitoring; TDM)을 추천한다. 본 연구의 목적은 포사코나졸 조기 TDM 및 용법변경이 정상상태(steady-state)에서의 적정 포사코나졸 혈장 농도(plasma posaconazole concentration; PPC)를 달성하는 것에 미치는 영향을 평가하는 것이다.

방법

2014년 9월부터 2016년 8월까지 서울대학교병원과 분당서울대학교병원에 입원한 급성 골수성 백혈병 또는 골수 이형성 증후군 환자 중 예방적 항진균제로 포사코나졸을 투여 받은 환자를 대상으로 전향연구를 시행하였다. 2014년 9월부터 2015년 12월까지는 포사코나졸 투여 3일째 TDM을 시행하되 PPC에 따른 용법변경을 하지 않았고 (대조군), 2016년 1월부터 2016년 8월까지는

약물 투여 시작 후 3일 째 TDM을 시행하여 PPC가 400 ng/mL 미만이면 투약용법을 200mg씩 하루 3회에서 200mg씩 하루 4회로 변경하였다(조기 TDM군). 정상상태에서의 적정 PPC는 아스페르길루스에 대한 최소억제농도를 고려하여 500 ng/mL 이상으로 정의하였다.

결과

전체 148명의 환자가 분석에 포함되었다(대조군 107명, 조기 TDM군 41명). 대조군 107명 중 21명에서 3일째 PPC는 400 ng/mL미만이었고, 이들 중 8일째 적정 PPC를 달성한 환자는 6명이었다(29%). 조기 TDM군 41명 중 4명에서 3일째 PPC가 400 ng/mL 미만이었고, 이 환자들을 대상으로 포사코나졸 투약 횟수를 증가시켰을 때, 8일째 적정 PPC를 달성한 환자는 3명이었다(75%). 양 군에서 3일째 PPC가 500 ng/mL 이상에 도달한 환자는 104명이었으며 이 중 6.7% (7/104)는 8일 째 PPC가 500ng/mL 미만으로 측정되었다.

결론

포사코나졸의 조기 TDM 및 약물용법변경은 정상상태에서의 적정 PPC를 달성하는 것에 도움이 될 수 있다.