The Genetic Polymorphism UGT1A4*3 Is Associated with Low Posaconazole Plasma Concentrations in Hematological Malignancy Patients Receiving the Oral Suspension

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ABSTRACT The metabolism of posaconazole is mediated mainly by uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes, especially UGT1A4. The aim of this study was to investigate the effects of genetic polymorphisms on the posaconazole plasma concentration (PPC). This prospective study was conducted from September 2014 to August 2016. We enrolled patients with acute myeloid leukemia or myelodysplastic syndrome treated with posaconazole oral suspension (200 mg) three times daily for fungal prophylaxis. The patients were examined for the multidrug resistance gene 1 3435C>T and 2677G>T/A variations and the UGT1A4*3 allele by direct sequencing of DNA from peripheral whole-blood samples. We defined poor absorbers to be those with PPCs of <200 ng/ml and the optimal PPC to be ≥700 ng/ml on day 8. The associations between genetic polymorphisms and the PPC were evaluated using multivariate logistic regression analysis including clinical variables. During the study period, 132 patients were enrolled. Six patients (4.5%) were defined as poor absorbers, and 49 patients (37.1%) did not reach the optimal PPC on day 8. In multivariate analysis, the independent risk factors for a poor absorber were at least one UGT1A4*3 allele (adjusted odds ratio [aOR], 18.81; 95% confidence interval [CI], 1.09 to 324.44; *P* = 0.043) and poor oral food intake (aOR per −100 kcal, 1.44; 95% CI, 1.04 to 1.99; *P* = 0.029). There was no statistically significant association between the genetic polymorphisms and achievement of the optimal PPC on day 8. The UGT1A4*3 polymorphism is an independent risk factor for being a poor absorber of posaconazole oral suspension in patients with hematological malignancies.

KEYWORDS posaconazole, low posaconazole plasma concentration, genetic polymorphisms, UGT1A4, fungal prophylaxis

Posaconazole oral suspension is a triazole antifungal agent approved by the Food and Drug Administration (FDA) for the treatment of oropharyngeal candidiasis and for the prophylaxis of invasive fungal infections in patients with neutropenia after induction chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) or in those with graft-versus-host disease after receiving hematopoietic stem cell transplantation. Posaconazole tablet and injection formulations have been

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approved by the FDA since 2013, but the posaconazole oral suspension is still widely used worldwide. However, the bioavailability of the posaconazole oral suspension is unpredictable due to factors such as the gastrointestinal environment and feeding conditions (1, 2). Previous studies showed that 44 to 76% of patients in Europe and North America and ~20% of Korean patients had posaconazole plasma concentrations (PPCs) of <500 ng/ml (3–5). A low PPC can lead to breakthrough fungal infections (4, 6); therefore, many studies have attempted to predict and improve the PPC and identify risk factors for a low PPC (6–8).

Posaconazole is mainly (~77%) eliminated fecally as the parent compound, and the remainder is excreted as glucuronidated derivatives in urine (9). Some *in vitro* studies found that the formation of posaconazole metabolites in human liver microsomes was mediated by uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes, especially UGT1A4, and genetic polymorphisms of UGT1A4 could change the metabolism of posaconazole (10). UGT enzymes are mainly expressed in the liver and the intestine. Human UGT1A4 is primarily expressed in the liver, both in the hepatocyte and in the biliary epithelium. In a previous study in South Korea, nine genetic polymorphisms of UGT1A4 were found. Among them, UGT1A4*3 at codon 48 (a T-to-G transversion at exon 1), changing a leucine to a valine (L48V, 142T>G), is known to be associated with the glucuronidation of various medications, and it is the most common polymorphism of UGT1A4 in the Korean population (11).

The polymorphism of UGT1A4 is associated with hepatic glucuronidation activity, depending on the substances. For example, in a Japanese study, the polymorphism of UGT1A4 was more efficient in glucuronidating clozapine, imipramine, and cyproheptadine than wild-type UGT1A4 but it was less efficient in glucuronidating tigogenin (12). However, the effect of the polymorphism of UGT1A4 on PPC has not been well studied.

In addition, an increase in posaconazole clearance by P-glycoprotein inducers, such as phenytoin and rifabutin, suggests that P-glycoprotein is involved in posaconazole excretion (13, 14). The expression of P-glycoprotein is dependent on the human multidrug resistance 1 (MDR1) gene. Therefore, genetic polymorphisms of these genes could also affect the metabolism of posaconazole. Previous studies have shown no correlation between genetic polymorphisms of the MDR1 gene and PPC in healthy volunteers (14, 15); however, to the best of our knowledge, no previous study has evaluated the correlation between genetic polymorphism of UGT1A4 and PPC. The aim of this study was to identify genetic polymorphisms influencing the posaconazole level in patients with hematological malignancies treated with the posaconazole oral suspension.

RESULTS

Patients. A total of 132 patients were enrolled from September 2014 to August 2016 (Fig. 1). All patients were Korean, and the mean age was 53.9 ± 13.1 years, 54.5% (72/132) of patients were male, and 91.7% (121/132) of patients had AML (Table 1). Seventeen patients (12.9%) took H₂ blockers, and six (4.5%) took proton pump inhibitors (PPIs). There were six patients with PPCs of <200 ng/ml on day 8. Among these poor absorbers, PPCs were measured for only three patients on day 15, and none of them reached the optimal PPCs. The numbers of patients who had at least one UGT1A4*3 allele, MDR1 3435C>T allele, and MDR1 2677G>T/A allele were 38 (28.8%), 82 (62.1%), and 100 (75.8%), respectively (Table 2). The numbers of poor absorbers among wild-type carriers ($n = 94$), heterozygous carriers ($n = 36$), and homozygous carriers ($n = 2$) of UGT1A4*3 allele were two, four, and zero, respectively.

Risk factors for being a poor absorber. Poor oral food intake and administration of an acid-lowering agent were statistically significant risk factors for being poor absorbers in univariate analysis ($P = 0.016$ and $P = 0.008$, respectively) (Table 3). In multivariate analysis, the risk factors for being a poor absorber were at least one UGT1A4*3 allele (adjusted odds ratio [aOR], 18.805; 95% confidence interval [CI], 1.090 to 324.440; $P = 0.043$) and poor oral food intake (aOR per –100 kcal, 1.437; 95% CI, 1.038 to 1.992; $P = 0.029$). A genetic polymorphism of MDR1 was not a significant risk

FIG 1 Study flow diagram.

factor for being a poor absorber. The mean PPC was 863.6 ± 611.6 ng/ml in patients with at least one UGT1A4*3 allele and $1,055.4 \pm 634.8$ ng/ml in patients with wild-type UGT1A4 ($P = 0.115$).

Risk factors for suboptimal drug levels. The statistically significant risk factors for a suboptimal PPC (<700 ng/ml) identified by univariate analysis were poor oral food intake, diarrhea of grade ≥ 2 , and administration of an acid-lowering agent (Table 4). Poor oral food intake (aOR per -100 kcal, 1.103; 95% CI, 1.020 to 1.190; $P = 0.013$) and administration of an acid-lowering agent (aOR, 2.383; 95% CI, 1.033 to 5.497; $P = 0.042$) were significant risk factors for an optimal PPC in multivariate analysis. The presence of at least one UGT1A4*3 allele tended to be related to suboptimal drug levels, although it was not a statistically significant risk factor (aOR, 2.199; 95% CI, 0.941 to 5.139; $P = 0.069$).

TABLE 1 Baseline patient characteristics^a

Characteristic	Values
Mean $\pm$ SD age (yr)	53.9 $\pm$ 13.1
No. (%) of male patients	72 (54.5)
No. (%) of patients with Korean ethnicity	132 (100)
Mean $\pm$ SD ht (m)	1.64 $\pm$ 0.82
Mean $\pm$ SD wt (kg)	63.4 $\pm$ 11.8
Mean $\pm$ SD body mass index (kg/m ²)	23.4 $\pm$ 3.5
No. (%) of patients with hematological disease	
AML	121 (91.7)
MDS	11 (8.3)
No. (%) of patients with acid-lowering agent use	23 (17.4)
H ₂ blocker	17 (12.9)
PPI	6 (4.5)
Mean $\pm$ SD PPC (ng/ml) on day 8	1000.2 $\pm$ 631.9
No. (%) of patients with the following PPC (ng/ml):	
<200	6 (4.5)
200–700	43 (32.6)
>700	83 (62.9)

^aData are for 132 patients. AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; PPC, posaconazole plasma concentration; PPI, proton pump inhibitor.

TABLE 2 Genotyping results and PPCs in the study population^a

Gene or gene location and polymorphism	No. (%) of patients	Mean $\pm$ SD PPC (ng/ml) on day 8	No. (%) of patients with PPC (ng/ml) of:		
			<200 (n = 6)	200–700 (n = 43)	>700 (n = 83)
UGT1A4					
TT	94 (71.2)	1,055.4 $\pm$ 634.8	2 (33.3)	29 (67.4)	63 (75.9)
GT	36 (27.3)	884.1 $\pm$ 621.2	4 (66.7)	12 (27.9)	20 (24.1)
GG	2 (1.5)	495.4 $\pm$ 227.2	0	2 (4.7)	0
MDR1 position 3435					
CC	50 (37.9)	1,012.8 $\pm$ 630.6	4 (66.7)	16 (37.2)	30 (36.1)
CT	64 (48.5)	1,001.9 $\pm$ 699.6	2 (33.3)	25 (58.1)	37 (44.6)
TT	18 (13.6)	959.2 $\pm$ 339.1	0	2 (4.7)	16 (19.3)
MDR1 position 2677					
GG	32 (24.2)	968.0 $\pm$ 686.8	3 (50.0)	12 (27.9)	17 (20.5)
GA	15 (11.4)	1,051.2 $\pm$ 649.1	1 (16.7)	4 (9.3)	10 (12.0)
GT	48 (36.4)	1,053.0 $\pm$ 685.5	1 (16.7)	18 (41.9)	29 (34.9)
TA	16 (12.1)	943.1 $\pm$ 689.2	1 (16.7)	6 (14.0)	9 (10.8)
TT	18 (13.6)	975.7 $\pm$ 327.3	0	1 (2.3)	17 (20.5)
AA	3 (2.3)	694.4 $\pm$ 327.0	0	2 (4.7)	1 (1.2)

^aData are for 132 patients. PPC, posaconazole plasma concentration.

DISCUSSION

To the best of our knowledge, this is the first study to unveil the association between genetic polymorphisms of UGT1A4*3 and being a poor absorber of the posaconazole oral suspension. A strength of this study is that it was performed in the clinical setting rather than in a clinical trial with healthy volunteers. The number of poor absorbers in this study was lower than that in other studies (16, 17) because a strict bundle approach, such as regular education and monitoring, was applied.

The UGT enzymes constitute a superfamily that catalyzes the glucuronidation of many compounds, and UGT1A4 is the main enzyme responsible for the glucuronidation of posaconazole (10). The individual variability in UGT1A4 activity may be due to genetic polymorphisms, such as the UGT1A4 L48V polymorphism, which is associated with higher glucuronidation activity *in vitro* (18). This polymorphism may influence the catalysis of various drugs, such as amitriptyline, clozapine, olanzapine, tamoxifen, imipramine, and lamotrigine (19). In previous studies, subjects with the UGT1A4*3 variant had higher glucuronidation of olanzapine and clozapine and formed substantially more glucuronidated metabolites (20, 21). In a study of lamotrigine in a Chinese population, the group that carried the wild type showed higher lamotrigine serum

TABLE 3 Clinical and genetic factors associated with being a poor absorber of posaconazole oral suspension^a

Variable	Univariate analysis		Multivariate analysis	
	aOR (95% CI)	P	aOR (95% CI)	P
Age (/yr)	0.986 (0.927–1.048)	0.641	1.038 (0.953–1.130)	0.396
Male sex	1.706 (0.301–9.653)	0.688		
Body mass index	1.144 (0.924–1.417)	0.218	1.127 (0.884–1.437)	0.334
At least 1 UGT1A4*3 allele	5.412 (0.948–30.906)	0.057	18.805 (1.090–324.440)	0.043
At least 1 2677G>T/A variation at MDR1	0.299 (0.057–1.562)	0.153		
At least 1 3435C>T variation at MDR1	0.288 (0.051–1.631)	0.199		
AML diagnosis	2.320 (0.246–21.838)	0.413		
Poor oral food intake (/–100 kcal) ^b	1.290 (1.048–1.587)	0.016	1.437 (1.038–1.992)	0.029
Oral mucositis grade $\geq$ 2 ^b		1.000		
Diarrhea grade $\geq$ 2 ^b	4.750 (0.786–28.695)	0.123	13.029 (0.515–329.875)	0.119
Use of acid-lowering agent ^b	14.091 (1.587–125.084)	0.008	8.299 (0.715–96.366)	0.091
Use of PPI	6.100 (0.572–65.044)	0.210		
Use of H ₂ blocker	7.000 (1.218–40.225)	0.030		

^aOR, adjusted odds ratio; CI, confidence interval; AML, acute myeloid leukemia; PPI, proton pump inhibitor.^bThe variables were evaluated 4 to 8 days after starting the drug.

TABLE 4 Clinical and genetic factors associated with a suboptimal plasma concentration of posaconazole^a

Variable	Univariate analysis		Multivariate analysis	
	aOR (95% CI)	P	aOR (95% CI)	P
Age (/yr)	0.989 (0.962–1.016)	0.403	0.993 (0.963–1.023)	0.638
Male sex	0.798 (0.393–1.621)	0.589		
Body mass index	0.958 (0.863–1.064)	0.421	0.954 (0.853–1.066)	0.404
At least 1 UGT1A4*3 allele	1.829 (0.848–3.944)	0.163	2.199 (0.941–5.139)	0.069
At least 1 2677G>T/A variation at MDR1	0.584 (0.260–1.310)	0.211		
At least 1 3435C>T variation at MDR1	0.821 (0.398–1.694)	0.711		
AML diagnosis	0.350 (0.072–1.690)	0.211		
Poor oral food intake (/–100 kcal) ^b	1.120 (1.041–1.205)	0.002	1.103 (1.020–1.190)	0.013
Oral mucositis grade $\geq 2^b$	1.756 (0.419–7.361)	0.468		
Diarrhea grade $\geq 2^b$	3.510 (1.103–11.172)	0.039	3.296 (0.905–12.002)	0.070
Use of acid-lowering agent ^b	2.912 (1.338–6.335)	0.009	2.383 (1.033–5.497)	0.042
Use of PPI	2.641 (0.426–16.390)	0.360		
Use of H ₂ blocker	2.862 (1.264–6.478)	0.012		

^aOR, adjusted odds ratio; CI, confidence interval; AML, acute myeloid leukemia; PPI, proton pump inhibitor.

^bThe variables were evaluated 4 to 8 days after starting the drug.

levels and better treatment responses than the group that carried the UGT1A4*3 variant, suggesting a more rapid metabolism of lamotrigine in subjects with the UGT1A4*3 variant (22). Likewise, the difference in the clearance of posaconazole according to genetic polymorphisms has not yet been studied, but the result of this study suggested that genetic polymorphism of UGT1A4 could increase the clearance of posaconazole by increasing the glucuronidation efficiency.

In our study, the UGT1A4*3 polymorphism was found to be a risk factor for being a poor absorber of posaconazole, whereas the genetic polymorphisms of the MDR1 gene had no correlation with the PPC. The UGT1A4*3 polymorphism may promote the metabolism of posaconazole, as with other drugs.

In the present study, a poor absorber of posaconazole was defined as a patient with a PPC of <200 ng/ml, which is associated with a high incidence of breakthrough fungal infections and a failure to reach the optimal PPC even after increasing the frequency of posaconazole administrations (5, 17). Therefore, early screening of these poor absorbers could help physicians choose other antifungal agents before unnecessary dose adjustment of posaconazole. Thus, it is clinically important to identify the risk factors for the poor absorbers for posaconazole.

In this study, 28.8% of patients had at least one UGT1A4*3 allele, 62.1% had MDR1 3435C>T, and 75.8% had MDR1 2677G>T/A. In other genetic studies targeting Koreans, 12.0% had at least one UGT1A4*3 allele, 51.9% had MDR1 3435C>T, and 82.9% had MDR1 2677G>T/A (11, 23). Various studies have shown differences in the frequency of genetic polymorphisms of UGT1A4 between ethnic groups; for example, the frequencies of genetic polymorphisms of UGT1A4 were 12.0 to 19.6% in Asians (11, 24), 11% in Caucasians (24), 9% in Germans (25), and 3.5% in Jordanians (26).

This study has a few limitations. First, the sample size was small. This factor may have hindered establishing a statistically significant association between the polymorphism of UGT1A4 and suboptimal PPCs. In addition, the *post hoc* power analysis showed that the power of this study was 55.9%, which was a major limitation. Second, all patients took the posaconazole oral suspension in our study. Our results should be validated with other formulations, such as posaconazole tablets, which can provide more stable absorption (27). Nonetheless, this study is the first prospective, real-world study to show the relation between the blood level of posaconazole and genetic polymorphisms.

In conclusion, the UGT1A4*3 polymorphism was an independent risk factor for being a poor absorber of the posaconazole oral suspension, even after adjustment for clinical factors, such as diet, gastrointestinal disturbances, and the use of acid-lowering agents, in patients with hematological malignancies.

MATERIALS AND METHODS

Patients. This study included patients aged ≥ 18 years old who underwent chemotherapy for AML or MDS and who were treated with a posaconazole oral suspension at 200 mg three times a day as a prophylactic antifungal agent from September 2014 to August 2016. It was conducted prospectively at two university-affiliated hospitals in South Korea (Seoul National University Hospital, Seoul, South Korea, and Seoul National University Bundang Hospital, Seongnam, South Korea). To maintain therapeutic drug levels, posaconazole was administered with a meal or nutritional supplement and one glass of acidic fluid (28). The use of an acid-lowering agent, including proton pump inhibitors (PPIs), was allowed if the attending physicians considered it essential for patient care. Daily dietary information was monitored prospectively for all enrolled patients, and this information was analyzed statistically with a unit of 100 kcal.

Patients were excluded if they refused to participate or if the steady-state PPC or genotype was not obtained for any reason. We defined poor absorbers to be subjects having a PPC of <200 ng/ml on day 8 (5). The optimal level was ≥ 700 ng/ml, based on pharmacokinetic data that reported a higher incidence of breakthrough invasive fungal infections in patients with posaconazole average steady-state plasma concentrations of <700 ng/ml (16). The severity of gastrointestinal tract dysfunction was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (v4.0) scale (29).

Informed written consent was obtained from every patient. This study was approved by the Institutional Review Boards of both study hospitals.

Determination of posaconazole plasma concentration. Posaconazole concentrations in plasma were determined using a validated liquid chromatography-electrospray ionization-tandem mass spectrometry method (with an Agilent 1260 high-performance liquid chromatography system [Agilent Technologies, Santa Clara, CA, USA] and an API 3200 Quadrupole system [Sciex, Framingham, MA, USA]). Blood samples collected for analyses were centrifuged at 3,000 rpm for 10 min at 4°C to separate the plasma. Plasma (100 μ l) was mixed with 100% acetonitrile and an internal standard (posaconazole-d4; Toronto Research Chemicals, Toronto, Ontario, Canada) in 50% methanol. After the solution was vortexed for 1 min and centrifuged at 12,000 rpm for 5 min at 4°C, the supernatant was transferred to an autosampling vial, and then 3 μ l was injected into a column (Kinetex C₁₈ column; 100 by 2.1 mm; particle size, 2.6 μ m; Phenomenex, Torrance, CA, USA) at 25°C. The mobile phase consisted of 0.1% formic acid in 10 mM ammonium formate and acetonitrile. Detection was performed by multiple-reaction monitoring at fragmentations of m/z 702.0 to 127.0 for posaconazole and m/z 706.0 to 127.0 for posaconazole-d4. The calibration curve was linear over the range of 50 to 4,000 ng/ml.

Genotyping. The genotypes of MDR1 3435C>T and MDR1 2677G>T/A were analyzed using TaqMan allelic discrimination assays on an ABI 7500 real-time PCR system (Applied Biosystems, Foster City, CA, USA). Genomic DNA was extracted from 200 μ l of peripheral whole blood from each patient, using a QIAamp DNA blood minikit (Qiagen GmbH, Germany). A total of 10 μ l of the PCR mixture was prepared with 5 μ l of 2 $\times$ TaqMan genotyping master mix, 0.5 μ l of 20 $\times$ drug metabolism genotyping assay mix, 3.5 μ l of DNase-free water, and 1 μ l of genomic DNA. Genotyping of MDR1 3435C>T (rs1045642; assay identifier, C_7586657_20) and MDR1 2677G>T/A (rs2032582; assay identifiers, C_11711720C_30 and C_11711720C_40) single nucleotide polymorphisms were performed with validated TaqMan genotyping assays (Applied Biosystems, Foster City, CA, USA). The PCRs were carried out as follows: initial denaturation at 95°C for 10 min and 50 cycles of denaturation at 92°C for 15 s and annealing/extension at 60°C for 1 min. The allelic discrimination results were determined after the amplification by performing an endpoint read. The 7500 real-time PCR system software (v2.0.6; Applied Biosystems, Foster City, CA, USA) was used for the data analysis.

DNA direct sequencing. We targeted the UGT1A4 L48V polymorphism (142T>G). The PCR method used to amplify the UGT1A fragments was developed using the University of California Santa Cruz *in silico* PCR tool (30). The final volume of the PCR mixture was 10 μ l. The PCR mixture consisted of 10 ng of DNA, 0.0005 mM each primer pair, 0.25 mM deoxynucleoside triphosphates, 3 mM MgCl₂, 1 μ l 1 $\times$ reaction buffer, and 0.25 U Taq DNA polymerase (Intron Biotechnology, Seongnam-Si, Gyeonggi-do, South Korea). The PCR conditions used were as follows: initial denaturation at 94°C for 5 min; 35 cycles of denaturation at 94°C for 30 s, annealing at 60°C for 30 s, and initial extension at 72°C for 30 to 60 s; and a final extension at 72°C for 10 min. The PCR products were purified using a MultiScreen384-PCR filter plate (Millipore, Billerica, MA, USA). The purified products were then sequenced using a BigDye Terminator cycle sequencing kit and an ABI 3730xl automated sequencer (Applied Biosystems, Foster City, CA, USA). The sequencing primers were the same as those used for the PCR amplification. Mutation analyses were performed using Phred, Phrap, Consed, and Polyphred (v5.04) software (31).

Statistics. Univariate analysis was performed to test for differences between groups, using Student's *t* test and the chi-square test or Fisher's exact test, depending on the variable type. A *P* value of <0.05 was considered statistically significant. Variables that showed a *P* value of <0.1 and possible confounding variables, including age, body mass index, and gastrointestinal disturbances, were also included in the multivariate analysis. Statistical analyses were performed using IBM SPSS Statistics software (v22.0; IBM Corp., Armonk, NY, USA).

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