Risk factors associated with decreased posaconazole plasma concentrations in hematology patients

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Abstract

Introduction: Posaconazole is used as prophylaxis of invasive fungal disease in immunocompromised hematological patients. During routine therapeutic drug monitoring of posaconazole, a large variability in posaconazole exposure within and between patients is repeatedly observed. This results in suboptimal plasma concentrations in a substantial part of the hematological patients. Posaconazole concentration <0.7 mg/L are associated with increased risk of invasive fungal disease. A few risk factors have been suggested to be associated with decreased posaconazole concentrations. The aim of this study is to identify risk factors that are associated with decreased posaconazole concentrations in hematology patients of The Hague Teaching Hospital, in order to adjust the prophylactic starting dose of patients who might benefit from a higher posaconazole starting dose proactively.

Methods: A retrospective cohort study was performed. Patients aged >18 years with a hematological malignancy who were initiated on posaconazole tablets prophylactically and had a plasma posaconazole concentration measured between January 2017 and December 2022 were included. The primary endpoint was the initial posaconazole plasma concentration (3-4 days) after initiation of the prophylactic treatment. Univariate and multivariate linear regression analysis were performed to identify variables that are associated with decreased posaconazole concentration.

Results: A total of 148 patients were included in the study. Males accounted for 59.5% of the population and the median age was 62.0 years (interquartile range 53.0-70.0). Subtherapeutic posaconazole concentrations (<0.7 mg/L) were observed in 23.9% of patients. At multivariate linear regression, body weight (p = <0.001), use of corticosteroids (p = 0.031), use of flucloxacillin (p = 0.047), lower albumin (p = 0.002) and glucose concentrations (p = 0.036) were significantly associated with decreased posaconazole concentrations, whereas a higher age (p = 0.033), diagnosis of ALL (p = <0.001) and treatment with a chemotherapy regimen existing of decitabine, venetoclax & midostaurin (p = 0.007) were associated with increased posaconazole concentrations in our patient population.

Conclusion: Hematology patients who have a higher body weight, lower albumin concentrations, lower glucose concentrations, use corticosteroids or flucloxacillin might benefit from a higher posaconazole starting dose for prophylactic treatment.

Nederlandse samenvatting

Introductie: Posaconazol wordt gebruikt als profylaxe van invasieve schimmelinfecties bij immuungecompromitteerde hematologische patiënten. Tijdens TDM van posaconazol werd een grote variabiliteit in de blootstelling aan posaconazol tussen en binnen patiënten waargenomen. Dit resulteert in suboptimale plasmaconcentraties bij een substantieel deel van de hematologische patiënten. Posaconazol concentraties <0,7 mg/l zijn geassocieerd met een verhoogd risico op invasieve schimmelinfecties. Enkele risicofactoren schijnen een associatie te hebben met verlaagde posaconazol concentraties. Het doel van deze studie is om de risicofactoren die geassocieerd zijn met verlaagde posaconazol concentraties bij hematologiepatiënten van het Haags Academisch Ziekenhuis te identificeren, zodat de profylactische startdosis van patiënten die baat zouden kunnen hebben bij een hogere posaconazol startdosis proactief aangepast wordt.

Methoden: Een retrospectief cohortonderzoek werd uitgevoerd. Patiënten ouder dan 18 jaar met een hematologische maligniteit die profylactisch met posaconazol tabletten behandeld worden en bij wie tussen januari 2017 en december 2022 een plasmaconcentratie van posaconazol werd gemeten, werden geïncludeerd. Het primaire eindpunt was de initiële plasmaconcentratie van posaconazol (3-4 dagen) na aanvang van de profylactische behandeling. Univariate en multivariate lineaire regressieanalyses werden uitgevoerd om de variabelen die geassocieerd zijn met verlaagde posaconazol concentraties te identificeren.

Resultaten: In totaal werden 148 patiënten geïncludeerd in de studie, waarvan 59,5% bestond uit mannen. De mediane leeftijd was 62,0 jaar (interkwartielafstand 53,0-70,0). Subtherapeutische posaconazol concentraties (<0,7 mg/l) werden waargenomen bij 23,9% van de patiënten. Bij multivariate lineaire regressie waren lichaamsgewicht (p = <0,001), gebruik van corticosteroïden (p = 0,031), gebruik van flucloxacilline (p = 0,047), lage albumine concentraties (p = 0,002) en lage glucose concentraties (p = 0,036) significant geassocieerd met een afname van posaconazol concentraties, terwijl leeftijd (p = 0,033), de diagnose ALL (p = <0,001) en chemotherapie met decitabine, venetoclax en midostaurine (p = 0,007) geassocieerd waren met verhoogde posaconazol concentraties in onze patiëntenpopulatie.

Conclusie: Hematologiepatiënten met een hoger lichaamsgewicht, lage albumine concentraties, lage glucose concentraties, corticosteroïden of flucloxacilline gebruik, kunnen baat hebben bij een hogere profylactische startdosis van posaconazol.

1 | Introduction

A large variability in posaconazole exposure is observed within and between patients (1). This results in suboptimal plasma concentrations in a substantial part of the hematological patients treated with the standard prophylactic dose (300 mg delayed-release tablet once a day). Not reaching an adequate posaconazole plasma concentration is a major problem in immunocompromised hematological patients. Posaconazole concentrations <0.7 mg/L are associated with increased risk of invasive fungal disease (IFD). IFD is difficult to treat because of the need of early therapeutic intervention and the emergence of resistance. Moreover, IFD remains a major cause of mortality in hematology patients (2, 3). A recent retrospective study carried out among adult hematologic patients and hematopoietic cell transplantation (HCT) recipients showed that the overall incidence of IFD's was 11.7%. The overall 6-week mortality rate in these patients with IFD was 37.2%. (4) It is not completely clear which patients are at risk for an inadequate posaconazole plasma concentration. Therefore, the prophylactic starting dose of patients who might benefit from a higher posaconazole starting dose, is not being adjusted proactively at this moment. Thus, a proportion of patients are at risk for a reduced exposure to posaconazole and therefore increased risk of IFD.

The posaconazole suspension formulation showed a high pharmacokinetic variability which often leads to suboptimal posaconazole concentrations. To overcome this limitation of suboptimal concentrations, delayed-release posaconazole tablets were developed. As a result, the oral bioavailability of posaconazole has increased. Still, variability in posaconazole exposure is observed. (2) Previous studies have shown that variability in posaconazole exposure is partly caused by factors affecting the absorbance (1, 5-11). Posaconazole is a highly lipophilic weak base. Co-administration of high-fat food therefore improves the absorbance and bioavailability of the suspension as well as the tablet. The co-administration of Coca-Cola with the posaconazole suspension has shown to significantly increase the posaconazole gastric concentrations with 102% and systemic exposure with 70% in healthy patients (12). Another risk factor for decreased posaconazole absorption is a gastric bypass, as this is associated with reduced gastric pH levels and a faster intestinal transit time (7, 13). Other important factors that influence the pharmacokinetics of posaconazole are presence of diarrhea and mucositis, common adverse reactions of chemotherapy (1, 14). Moreover, concomitant use of medication that affects gastric pH may also influence posaconazole exposure. Increased gastric pH levels result in an unpredicted bioavailability and sub-therapeutic plasma concentrations of posaconazole. A retrospective study showed a reduction of Cmin with 45% during concomitant treatment with proton pump inhibitors (PPI's) (2). A prospective study has shown that famotidine is a significant risk factor for low plasma concentrations (<0.7mg/l) (15). Seriously ill patients with hematological disorders usually have an increased gastric pH level, because these patients commonly use acid-suppressive agents like esomeprazole for the treatment of gastric ulcers or stress related mucosal disease. Thus, these patients are likely to exhibit decreased posaconazole absorption (9, 10, 16). In immunocompromised patients, co-administration of metoclopramide was also proven to reduce the bioavailability of posaconazole by 35% (5). Based on this information, it could be suggested that a different posaconazole dosing regimen may be useful in patients treated with PPIs, famotidine and/or metoclopramide.

The variability in posaconazole concentrations could also be the result of differences in posaconazole distribution between patients. Posaconazole is highly plasma protein bound. Therefore, hypoalbuminemia may result in increased free fraction of posaconazole, leading to decreased total plasma concentrations. However, studies show contradictory results. Hypoalbuminemia seems to influence the posaconazole exposure significantly in several studies (5, 7, 11, 17), but in a study of Prayag et. al

hypoalbuminemia is not found to be significant for the tablet (10). In addition to hypoalbuminemia, body weight may also influence the distribution and therefore the plasma concentrations of posaconazole. Tang et. al showed that male patients treated with the tablets have significantly lower posaconazole plasma concentrations than female patients. According to Tang et. al, an explanation for lower plasma concentrations in males could be their higher body weight and different habitus, which attributes to an increased distribution volume and clearance (CL) of posaconazole (18). Tang et al. also showed significant lower plasma concentrations by patients weighing >90 kg (11). In contrast, in the study of Prayag et. al obesity is not found to be a significant factor for low plasma concentrations with the tablet (10), while Chen et al. showed significantly lower plasma concentrations in obese patients (5).

The variability in posaconazole concentrations could also be the result of differences in posaconazole metabolism and elimination between patients. Posaconazole is metabolized predominantly by UDP-glucuronosyltransferase 1-4 (UGT1A4) glucoronidation. Corticosteroids and flucloxacillin are found to decrease posaconazole concentrations, possibly as result of altered metabolism. A retrospective study showed a reduction of Cmin with 44% during concomitant treatment with steroids, possibly as a result of increased UGT1A4 activity (2). Also, in patients that are concomitantly treated with flucloxacillin, decreased posaconazole concentrations were observed (19). An explanation for this observation is the increased elimination and decreased absorption of posaconazole as a result of induced P-glycoprotein (P-gp) expression by flucloxacillin. Posaconazole is both substrate and inhibitor for P-gp. Induced P-gp expression by flucloxacillin may be the cause of decreased posaconazole concentrations. (19-21)

All of the various factors mentioned above may possibly lead to a reduced exposure to posaconazole, but causal factors remain unclear for the posaconazole tablets in our patient population. First, some of the data mentioned above is contradictory. Several studies for instance demonstrate that posaconazole exposure does not appear to be significantly affected by co-medication (1, 15, 22-25). Additional research is needed to formulate a statement about potential drug-drug interactions. Second, some of the factors mentioned above are also only studied with the suspension so it is unclear whether they also apply to the tablet, which is used at Hague Teaching Hospital. Third, some of the outcomes are based on healthy volunteers or other patients than hematology patients. Healthy populations avoid the interferences of pathological factors on absorption. Food intake for example is often not feasible in patients in comparison with healthy volunteers, which probably leads to an even lower exposure in patients (1). In addition, Dolton et. al (2014) showed a 55% lower relative bioavailability of posaconazole in patients than in healthy volunteers (6). For instance, the study of Jansen et al. only included patients who had undergone an allogeneic stem cell transplant, while other hematological patients undergoing intensive chemotherapy for acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) or acute lymphocytic leukaemia (ALL), were not included. It is possible that hematological conditions or treatment schedules influence the posaconazole concentrations. In the study of Tang et al. for instance, patients with AML had lower sub therapeutic concentrations (15%) compared with the non-AML cohort (32%) (11). Besides, the study only studied the influence of severe mucositis on the bioavailability of posaconazole. The influence of mild and moderate mucositis has been disregarded. Notably, the influence of co-medication on posaconazole exposure was also not taken into account in the analysis. Most people who receive posaconazole are hematology patients and it is important to conduct additional research with all the possible factors on this specific patient population.

To answer our research question “which hematology patients might benefit from a higher posaconazole starting dose for prophylactic treatment?”, the aim of this study was to identify risk factors that are associated with decreased posaconazole concentrations in hematology patients of The Hague Teaching Hospital.

2 | Methods

2.1 | Study design and participants

A retrospective study was conducted in the Hague Teaching Hospital in the Netherlands. The correlation between posaconazole plasma concentrations and various patient-, medication- and disease-related factors were investigated. Patients aged >18 years with a hematological malignancy who were initiated on posaconazole tablets prophylactically and had a plasma posaconazole concentration measured between January 2017 and December 2022 were included. The exclusion criteria were incorrect timing (<3 days after initiation) of posaconazole concentration measurements and documented history of not wanting to participate in any kind of research. The primary outcome is the initial posaconazole plasma concentration (3-4 days) after initiation of the prophylactic treatment. The prophylactic treatment consists of a loading dose of 300 mg twice daily for one day, followed by 300 mg once daily. As standard care, plasma concentrations are measured 3-4 days after starting posaconazole treatment. We obtained a waiver for the Medical Research Involving Human Subjects Act from the Medical Ethical Review Committee Leiden The Hague Delft (METC LDD/METC-number: N22.062). No informed consent from the included patients was needed.

2.2 | Variables and data collection

Data about sex, age, height, weight, BMI, indication, chemotherapy regimen, initial posaconazole plasma concentrations, occurrence of mucositis, occurrence of diarrhea, gastric bypass, TPV use, various laboratory data and the use of the co-medications antacids, proton pump inhibitors, H2 antagonists, antiemetics, corticosteroids, flucloxacillin, venetoclax and tyrosine kinase inhibitors were collected from the hospital's electronic information system using CT-cue datamining software (CTcue B.V., Amsterdam, The Netherlands). Some data is collected from the Cytostatics Management System (CMS). The data is stored and secured in Excel. Data on demographics were all extracted around the time of posaconazole measurements and data on laboratory values were extracted maximal 2 weeks prior to posaconazole measurements. Corticosteroid dose regimens were categorized into two groups based on the clinical dosing regimens equivalent to prednisolone (low if ≤30 & high if >30 mg per day) (26). A number of patients had a corticosteroid dose 'according to reduction schedule'. Because of this, the dose of the corticosteroids may have been higher earlier than at the time of posaconazol plasma concentration measurements. In case of corticosteroid reduction schedule, the dose of 3 days before posaconazole plasma concentrations was consistently assumed. The chemotherapy treatments were divided into seven categories based on medication similarities (table S1, see supplementary materials). Indication was divided into three categories: AML, ALL and others (Chronic myeloid leukemia (CML); RAEB; Multiple myeloma (MM); Non Hodgkin lymfoom intermediate/high grade (NHL); Chronic myelomonocytic leukemia (CMML); myeolodysplasia (MDS); Other lymphoproliferative disorders). The indications other than AML and ALL were combined, because separately they consisted a small number of patients. There are three standard indications for prophylaxis with posaconazole. These are: ALL according to HOVON 100 protocol, AML/MDS and >3 weeks of neutropenia due to decitabine treatment. However, some patients had other indications due to increased risk.

2.3 | Data analysis

The analysis was performed using SPSS version 28.0 for Windows. Descriptive statistics for continuous variables were reported as the mean ± standard deviation (SD) in case of normally distributed variables,

and as the median number with interquartile range (IQR) in case of non-normally distributed variables. Visual data inspection was performed using histograms, QQ-plots and boxplots for outliers to assess whether clinical data were normally distributed. Descriptive statistics for categorical variables were noted as frequencies and percentages per category. Missing values are considered 'Missing Completely At Random' and were ignored if the number was small (<10%). Variables were omitted from analysis if more than 20% of the values were missing.

Univariate and multivariate linear regression analysis were performed in order to assess the potential correlation between the initial posaconazol concentration and the variables. The assumptions for linear regression were checked. The homogeneous distribution and linear relationship between posaconazole and variables were verified using scatter plots. Variables were included in the multivariate linear regression model if they were associated with $p \leq 0.200$ in the univariate analysis. In the multivariate analysis with stepwise backwards deletion a p-value $p < 0.05$ was considered statistically significant. Variables were deleted using a backward deletion procedure ($p > 0.05$ for removal) to create the final model.

3 | Results

3.1 | Characteristics of the population

In total, 163 patients met the inclusion criteria. After data validation, 15 patients were excluded due to incorrectness of posaconazole plasma concentration measurements. 14 patients were excluded because of incorrect timing of posaconazole concentration measurements (<3 days after initiation) and 1 patient was excluded because the posaconazole concentration measurement was unjustified and he was not using posaconazole. Thus, 148 patients were included in the study. Data about CRP values was missing in 14.9% of the patients. The following data was missing in more than 20% and is not included in the statistical analysis: iron in 64.9%, ferritin in 54.7%, vitamin B12 and folic acid in 58.8%. Patient demographics and clinical characteristics are summarized in Table 1. Males accounted for 59.5% of the population and the median age was 62.0 years (interquartile range [IQR] 53.0-70.0). Median body weight of the cohort was 82.9 kg (IQR 70.5-90.6). The most frequent underlying diseases were AML (68.2%) and ALL (20.3%). The median time to first posaconazole measurement after initiation of posaconazole was 4 days (IQR 3.0-7.0) and the median posaconazole concentration at first measurement was 1,0 mg/L (IQR 0.7-1.5). 23,9% of the posaconazole concentrations were <0.7 mg/L.

Table 1 Patient demographics and posaconazole treatment[a,b]

Total number of patients	148
Age (years)	62 (53.0-70.0)
Gender (M/F)	88/60
Weight (kg)	82.9 (70.5-90.6)
Height (cm)	176.0 (166.3-182.0)
Body mass index (kg/m2)	26.2 (23.2-29.6)
Albumin (g/L)	34.0 (32.0-39.0)
Underlying hematological disease	
AML	101 (68.2)
ALL	30 (20.3)
CML	2 (1.4)
RAEB	3 (2)
MM	1 (0.7)
NHL	4 (2.7)
Other	7 (4.7)
Posaconazole treatment	
Time (days) to first TDM Assessment	4 (3-7)
Cmin (mg/L) at first TDM Assessment	1 (0.7-1.5)
Co-treatment	
PPI	121 (81.8%)
H2 antagonists	2 (1.4%)
Antacids	8 (5.4%)
Corticosteroids	71 (48%)
Antiemetic's	122 (82.4%)
TPV	4 (2.7%)
Flucloxacillin	7 (4.7%)
Tyrosine kinase inhibitors/venetoclax	11 (7.4%)

Kind of corticosteroid use	
Dexamethason	34 (23.0%)
Prednisolon	37 (25.0%)
Dose of corticosteroids	
Low dose	39 (26.4%)
High dose	32 (21.6%)
Diarrhea	65 (43.9%)
Mucositis	71 (48.0%)
Gastric bypass	2 (1.4%)
Chemotherapy regimen	
Treatment group 1	63 (42.6 %)
Treatment group 2	13 (8.8%)
Treatment group 3	18 (12.2%)
Treatment group 4	20 (13.5%)
Treatment group 5	8 (5.4%)
Treatment group 6	7 (4.7%)
Treatment group 7	19 (12.8%)

[a] Data for continuous variables are presented as median (IQR), and data for categorical variables are presented as number (%).
[b] Abbreviations: AML, acute myeloid leukaemia; ALL, acute lymphocytic leukaemia; CML, chronic myeloid leukemia; MM, multiple myeloma; NHL, Non Hodgkin lymfoom intermediate/high grade; TDM, therapeutic drug monitoring; Cmin, posaconazole trough concentration; IQR, interquartile range.

3.2 | Risk factors

Age, body weight, leukocytes, creatinine, eGFR, albumin, GGT, glucose, diarrhea, mucositis, gastric bypass, concomitant PPI use, concomitant corticosteroid use, concomitant flucloxacillin use, low dose corticosteroids, diagnosis and chemotherapy regimen were associated with $p \leq 0.200$ in the univariate analysis and were included in the multivariate linear regression analysis. Posaconazole plasma concentrations were not normally distributed and therefore log-transformed. Results are reported in Table 2. The final model after backwards deletion contained age, body weight, albumin, glucose, ALL, concomitant corticosteroids use, concomitant flucloxacillin use and treatment with a chemotherapy regimen existing of decitabine, venetoclax & midostaurin. The overall p-value in the final model was 0,001 and the adjusted R^2 was 0,222.

Multivariate analysis showed that in patients receiving the posaconazole tablets, body weight, co-treatment with corticosteroids or with flucloxacillin, lower albumin and glucose concentrations were associated with a reduction in posaconazole plasma concentrations. Conversely, age, diagnosis of ALL and treatment with a chemotherapy regimen existing of decitabine, venetoclax & midostaurin were associated with an increase (ranging from 0.3% to 31.7%) in posaconazole concentrations in our patient population. Other variables were not found to be significantly associated with posaconazole plasma concentrations in our patient cohort.

Overall, a statistically significant decrease of posaconazole concentration was observed in relation to systemic corticosteroid use in both univariate as multivariate analysis. Univariate analysis also revealed that low dose corticosteroid use and use of dexamethasone decreased the posaconazole concentrations (table S2, table S3). However, a statistical interaction between dose of corticosteroids and posaconazole concentrations was not seen in the final model.

Table 2 Univariate and multivariate linear regression analysis to investigate the association between variables and posaconazole Cmin (n = 148) [a]

Variables	Univariate analysis		Multivariate analysis	
	Unstandardized β-coefficient (95% CI)	*P*	Unstandardized β-coefficient (95% CI)	*P*
Male sex	0 (ref.)			
Female sex	0.040 (-0. 049, 0.128)	0.376	–	
Age (years)	0.003 (0.000, 0.005)	0.081	0.003 (0.000, 0.006)	0.033
Weight (kg)	-0.002 (-0.004 , 0.001)	0.009	-0.004 (-0.006, -0.002)	<0.001
Height (cm)	-0.002 (-0.006, 0.003)	0.480	–	
Body mass index (kg/m2)	-0.005 (-0.013, 0.003)	0.260	–	
Time (days) to first TDM Assessment	0.012 (-0.014, 0.038)	0.370	–	
Laboratory data				
Albumin (g/L)	0.008 (0.000, 0.016)	0.041	0.012 (0.005, 0.020)	0.002
Hemoglobin	0.026 (-0.015, 0.066)	0.214	–	
Leukocytes	0.006 (-0.002, 0.014)	0.166	0.005 (-0.003, 0.012)	0.217
Creatinine	0.002 (0.000, 0.004)	0.034	0.000 (-0.002, 0.002)	0.846
Egfr	-0.002 (-0.004, 0.000)	0.039	0.000 (-0.006, 0.005)	0.883
ALAT	-0.00006 (-0.001, 0.000)	0.818	–	
ASAT	0.000 (-0.001, 0.001)	0.659	–	
LD	-0.000003 (0.000, 0.000)	0.885	–	
GGT	0.000 (-0.001, 0.000)	0.151	-0.00009 (0.000, 0.000)	0.529
Bilirubin	-0.001 (-0.005, 0.003)	0.495	–	
Alkalic phosphatase	0.000 (-0.001, 0.000)	0.214	–	
Ureum	0.002 (-0.012, 0.015)	0.783	–	
Glucose	0.010 (-0.005, 0.025)	0.190	0.016 (0.001, 0.030)	0.036
Phosphate	-0.029 (-0.200, 0.142)	0.737	–	
CRP	0.000 (-0.001, 0.000)	0.401	–	
Hematological disease				
Other [b]	0 (ref.)			
AML	0.111 (-0.023, 0.245)	0.104	0.094 (-0.038, 0.226)	0.162
ALL	0.173 (0.015, 0.330)	0.032	0.317 (0.149, 0.486)	<0.001
PPI				
No PPI use	0 (ref.)			
PPI use	-0.104 (-0.190, -0.019)	0.017	-0.045 (-0.129, 0.038)	0.284
H2 antagonists				
No H2 antagonist use	0 (ref.)			
H2 antagonist use	-0.081 (-0.459, 0.296)	0.671	–	
Antacids				
No antacid use	0 (ref.)			
Antacid use	0.023 (-0.170, 0.216)	0.816	–	
Corticosteroids				
No corticosteroid use	0 (ref.)			
Corticosteroid use	-0.059 (-0.146, 0.028)	0.182	-0.105 (-0.200, -0.010)	0.031
Dose				
Low dose	0 (ref.)			

High dose	0.117 (-0.008, 0.242)	0.067	0.014 (-0.200, 0.229)	0.896
No use	0.112 (0.009, 0.214)	0.034	-0.005 (-0.382, 0.371)	0.978
Kind of corticosteroid use				
Dexamethason	0 (ref.)			
Prednisolon	0.102 (-0.022, 0.227)	0.107		
No use	0.112 (0.004, 0.220)	0.042	–	
Antiemetic's				
No antiemetic use	0 (ref.)			
Antiemetic use	0.015 (-0.100, 0.129)	0.797	–	
TPV				
No TPV use	0 (ref.)			
TPV use	-0.020 (-0.289, 0.249)	0.885	–	
Flucloxacillin				
No flucloxacillin use	0 (ref.)			
Flucloxacillin use	-0.280 (-0.480, -0.079)	0.007	-0.197 (-0.392, -0.003)	0.047
Tyrosine kinase inhibitors/ venetoclax				
No use	0 (ref.)			
use	0.065 (-0.101, 0.231)	0.441	–	
Diarrhea				
No diarrhea	0 (ref.)			
Diarrhea	-0.073 (-0.160, 0.015)	0.102	0.014 (-0.078, 0.107)	0.760
Mucositis				
No mucositis	0 (ref.)			
Mucositis	-0.068 (-0.155, 0.018)	0.122	-0.035 (-0.122, 0.052)	0.421
Gastric bypass				
No gastric bypass	0 (ref.)			
Gastric bypass	-0.025 (-0.631, 0.121)	0.182	-0.132 (-0.598, 0.334)	0.576
Chemotherapy regimen [c]				
Treatment group 5	0 (ref.)			
Treatment group 1	0.254	0.009	0.155 (-0.022, 0.332)	0.086
Treatment group 2	0.296	0.011	0.122 (-0.100, 0.343)	0.279
Treatment group 3	0.457	<0.001	0.292 (0.083, 0.501)	0.007
Treatment group 4	0.303	0.005	0.059 (-0.163, 0.281)	0.598
Treatment group 6	0.339	0.012	0.156 (-0.084, 0.397)	0.200
Treatment group 7	0.268	0.014	0.165 (-0.037, 0.367)	0.109

[a] Abbreviations: Cmin, posaconazole trough concentration; TDM, therapeutic drug monitoring; AML, acute myeloid leukaemia; ALL, acute lymphocytic leukaemia; PPI, proton pump inhibitors

[b] Other = Chronic myeloid leukemia (CML); RAEB; Multiple myeloma (MM); Non Hodgkin lymfoom intermediate/high grade (NHL); Chronic myelomonocytic leukemia (CMML); myeolodysplasia (MDS); Other lymphoproliferative disorders.

[c] See table S1 for the contents of the treatment groups.

4 | Discussion

In this retrospective cohort study, we investigated the association of various patient-, medication- and disease-related factors with posaconazole plasma concentrations in 148 hematology patients in Hague Teaching Hospital in the Netherlands. A substantial part of the population did not reach an adequate posaconazole plasma concentration (23,9%). We found that body weight, co-treatment with corticosteroids or with flucloxacillin, lower albumin concentrations and lower glucose concentrations were associated with a reduced posaconazole plasma concentrations. A higher age, ALL diagnosis and treatment with a chemotherapy regimen existing of decitabine, venetoclax & midostaurin were associated with increased posaconazole plasma concentrations.

These results corroborate the findings of some of the previous work. Our study confirms the association between decreased posaconazole plasma concentrations and co-treatment with corticosteroids and with flucloxacillin (19). The finding about lower albumin concentrations being associated with decreased posaconazole concentrations is also consistent with that of Chen et al. (5) and Tang et. al (11) who stated the significant influence of hypoalbuminemia on posaconazole exposure. The finding simultaneously contradicts the findings of Prayag et. al (10). This suggests that pre-treatment serum albumin could be an important independent predictive marker. The results about body weight reflect those of Tang et. al who also found that higher body weight leads to lower posaconazole concentrations. A possible explanation for lower plasma concentrations in patients with a higher body weight might be the increased distribution volume and clearance of posaconazole in these patients.

However, the findings of our study do not support some of the previous research. It has been suggested that male patients have significantly lower posaconazole plasma concentrations than female patients (11). This does not appear to be the case in our study. The difference in findings might be caused by the small difference in body weight between the genders in our patient population. Furthermore, in contrast to earlier findings, we found no evidence of decreased posaconazole concentrations during concomitant use of medication that affects gastric pH. This is a particularly surprising result. Acid-suppressive agents are known to increase the gastric pH levels. Posaconazole, a highly lipophilic weak base, was therefore expected to exhibit decreased absorption. Patients using acid-suppressive agents may have been consuming Coca-Cola, which compensates the increase in gastric pH caused by acid-suppressive agents. This may explain why we did not found an association between posaconazole concentrations and medication that affects gastric pH. Another unexpected but important finding was that high dose corticosteroids did not tend to be associated with decreased risk of posaconazole concentrations, while systemic corticosteroid use independently appeared to significantly decrease posaconazole concentrations. A possible explanation for this finding could be the coherence with other factors. The finding may depend on the dosage, but also on the type of corticosteroid. It stands out that patients who received prednisolone usually had a high dose, while patients receiving dexamethasone usually had a low dose. Because of this, we only included dosage of corticosteroid in the analysis and did not include kind of corticosteroid. Dosage seems to be a confounder. Mucositis is also not found to be significantly associated with posaconazole plasma concentrations in our patient cohort. This is not in line with the results of Jansen et al. who stated the significant influence of mucositis in posaconazole exposure. This contrast might be related to the differences in the study designs. The study of Jansen et al. was prospective and only studied the influence of severe mucositis on the bioavailability of posaconazole. Our study was retrospective and therefore a distinction between severe, moderate and mild mucositis was not possible. Furthermore, in our study patients with AML did not show a significant association with decreased

posaconazole concentrations compared to ALL or other indications. This is not in line with the study of Tang et al. who found that patients with AML had lower sub therapeutic concentrations (15%) compared with the non-AML cohort (32%). Nevertheless, patients with ALL did show a significant association with increased posaconazole concentrations.

Glucose, age and a chemotherapy regimen existing of decitabine, venetoclax & midostaurin were also significantly associated with increased posaconazole plasma concentrations. The association of age with increased posaconazole plasma concentrations might be related to reduced clearance in eldery. However, renal elimination is only a minor excretion pathway of posaconazole and thus negligible compared to the mean total body clearance (27). A possible explanation for the association of glucose with increased posaconazole plasma concentrations, is the association with body weight. Patients with a higher body weight and diabetics may have an increased distribution volume and clearance of posaconazole.

In clinical practice, posaconazole concentrations <0.7 mg/L are associated with increased risk of invasive fungal disease. A higher body weight, lower albumin concentrations, lower glucose concentrations and concomitant treatment with corticosteroids or flucloxacillin increases the risk of an inadequate posaconazole plasma concentration and therefore IFD.

This study has several limitations. The retrospective nature of this study and the limited sample size may limit the generalizability of the findings. In addition, data collection of some of the variables was impossible as e.g. data about food intake could not be traced. Also, Coca-Cola was not taken before the initial posaconazole plasma concentration, which is the primary outcome, and could therefore not be taken into account in this study. It must be analyzed for other secondary outcomes. Furthermore, our method can be sensitive to multiple testing and therefore, there is a chance of finding false-positive results. Diagnosis of ALL and chemotherapy regimens existing of decitabine, venetoclax & midostaurin may be examples of false-positive results. However, this study was exploratory and with further prospective research we could test whether dose adjustments actually lead to more adequate posaconazole plasma concentrations.

With this study, we identified risk factors that are associated with decreased posaconazole concentrations in hematology patients of The Hague Teaching Hospital. Our work suggests that hematology patients who have a higher body weight, lower albumin concentrations, lower glucose concentrations, concomitant treatment with corticosteroids or with flucloxacillin might benefit from a higher posaconazole starting dose for prophylactic treatment. Further prospective studies are required to confirm the results found in this study. More data will be obtained with a prospective study design and this will allow us to better assess some of the variables, like mucositis and PPI's. A prospective study can also confirm whether dose adjustments actually lead to more adequate posaconazole concentrations and whether a dose increase from 300 mg once a day to 400 mg once a day is sufficient enough.

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Supplementary materials

Table S1 Categories of chemotherapy regimens

Categories of chemotherapy regimens are based on medication similarities. The chemotherapy regimens are combined in a treatment group if they consist the same medication.

Category	Chemotherapy regimens	Main medication
Treatment group 1	*[o]H150:* Daunorubicine Cytarabine *H100:* Cytarabine PEG-Asparaginase (Oncospar) Rituximab Methotrexate Dexamethasone *H103:* Daunorubicine Cytarabine *AMCA-ARA-C:* Daunorubicine Cytarabine *CYTA40 IT:* Cytarabine Dexamethasone *H102:* Amsacrine Cytarabine	Cytarabine
Treatment group 2	*APL:* Arseentrioxide Tretinoïde *Vidaza:* Azacitidine *CHOP:* Cyclofosfamide Doxorubicine Vincristine Prednisolon *H146:* Blinatumomab	Other
Treatment group 3	*Decitabine* *H155:* Decitabine Midostaurin	Venetoclax/decitabine

	H135: Decitabine *Venetoclax 100mg, Venetoclax/decitabine*	
Treatment group 4	*Prephase H100:* Prednison Methotrexate/ dexamethason *Prephase unfit elderly schedule with Philadelphia Chromosome-positive precursor:* *Prephase unfit elderly schedule with Philadelphia Chromosome-negative precursor*: Prednison Methotrexate Dexamethason *Methotrexate/Dexamethasone*	Prednison Methotrexate Dexamethason
Treatment group 5	*H156:* Mitoxantrone Etoposide + Midostaurin or Gilteritinib *HDM:* High dose Melfalan *BEAM:* Carmustine Etoposide Cytarabine Melfalan *MBVP:* MethotrexatE Teniposide Carmustine Prednisolone Folinicacid	Melfalan, etoposide, carmustine
Treatment group 6	*EORTC*	Gemcitabine, cisplatine, lapatinib

	Gemcitabine Cisplatine Lapatinib	
Treatment group 7		Lenalidomide
	H132: Lenalidomide	

[a] *H= HOVON*

Table S2 Univariate analysis of dose of corticosteroids with dummy variables

Three dummy variables are made for the categorical variable 'dose of corticosteroids'. Those dummy variables are used to compare all of the categories with each other.

	Univariate analysis	
Variables	**Unstandardized β-coefficient (95% CI)**	***P***
Model 1		
No use	0 (ref.)	
Low dose	-0.112 (-0.214, -0.009)	0.034
High dose	0.005 (-0.105, 0.115)	0.926
Model 2		
Low dose	0 (ref.)	
High dose	0.117 (-0.008, 0.242)	0.067
No use	0.112 (0.009, 0.214)	0.034

Table S3 Univariate analysis of kind of corticosteroid use with dummy variables

Three dummy variables are made for the categorical variable 'kind of corticosteroids'. Those dummy variables are used to compare all of the categories with each other.

	Univariate analysis	
Variables	**Unstandardized β-coefficient (95% CI)**	***P***
Model 1		
No use	0 (ref.)	
Dexamethason	-0.112 (-0.220, -0.004)	0.042
Prednisolon	-0.010 (-0,115, 0.095)	0.851
Model 2		
Dexamethason	0 (ref.)	
Prednisolon	0.102 (-0.022, 0.227)	0.107
No use	0.112 (0.004, 0.220)	0.042

Table S4 Univariate analysis of diagnosis with dummy variables

Three dummy variables are made for the categorical variable 'diagnosis'. Those dummy variables are used to compare all of the categories with each other.

	Univariate analysis	
Variables	**Unstandardized β-coefficient (95% CI)**	***P***
Model 1		
ALL	0 (ref.)	
AML	-0.062 (-0.172, 0.049)	0.272
Other	-0.173 (-0.330, 0.015)	0.032
Model 2		
Other	0 (ref.)	
AML	0.111 (-0.023, 0.245)	0.104
ALL	0.173 (0.015, 0.330)	0.032

Table S5 Univariate analysis of chemotherapy regimens with dummy variables

Seven dummy variables are made for the categorical variable 'chemotherapy regimens'. Those dummy variables are used to compare all of the categories with each other.

	Univariate analysis	
Variables	**Unstandardized β-coefficient (95% CI)**	***P***
Treatment group 1	0 (ref.)	
Treatment group 2	0.042 (0.113, 0.196)	0.594
Treatment group 3	0.203 (0.068, 0.339)	0.004
Treatment group 4	0.049 (-0.081, 0.179)	0.456
Treatment group 5	-0.254 (-0.444, -0.064)	0.009
Treatment group 6	0.085 (-0.117, 0.287)	0.406
Treatment group 7	0.014 (-0.118, 0.147)	0.833
Treatment group 2	0 (ref.)	
Treatment group 1	-0.042 (-0.196, 0.113)	0.594
Treatment group 3	0.162 (-0.023, 0.346)	0.085
Treatment group 4	0.007 (-0.173, 0.188)	0.935
Treatment group 5	-0.296 (-0.523, -0.068)	0.011
Treatment group 6	0.044 (-0.194, 0.281)	0.718
Treatment group 7	-0.028 (-0.210, 0.155)	0.766
Treatment group 3	0 (ref.)	
Treatment group 1	-0.203 (-0.339, -0.068)	0.004
Treatment group 2	-0.162 (-0.346, 0.023)	0.085
Treatment group 4	-0.154 (-0.319, 0.011)	0.066
Treatment group 5	-0.457 (-0.673, -0.242)	<0.001
Treatment group 6	-0.118 (-0.344, 0.108)	0.303
Treatment group 7	-0.189 (-0.356, -0.022)	0.026
Treatment group 4	0 (ref.)	
Treatment group 1	-0.049 (-0.179, 0.081)	0.456
Treatment group 2	-0.007 (-0.188, 0.173)	0.935

Treatment group 3	0.154 (-0.011, 0.319)	066
Treatment group 5	-0.303 (-0.515, -0.091)	0.005
Treatment group 6	0.036 (-0.187, 0.259)	0.749
Treatment group 7	-0.035 (-0.197, 0.127)	0.671
Treatment group 5	0 (ref.)	
Treatment group 1	0.254 (0.064, 0.444)	0.009
Treatment group 2	0.296 (0.068, 0.523)	0.011
Treatment group 3	0.457 (0.242, 0.673)	<0.001
Treatment group 4	0.303 (0.091, 0.515)	0.005
Treatment group 6	0.339 (0.077, 0.601)	0.012
Treatment group 7	0.268 (0.055, 0.482)	0.014
Treatment group 6	0 (ref.)	
Treatment group 1	-0.085 (-0.287, 0.117)	0.406
Treatment group 2	-0.044 (-0.281, 0.194)	0.718
Treatment group 3	0.118 (-0.108, 0.344)	0.303
Treatment group 4	-0.036 (-0.259, 0.187)	0.749
Treatment group 5	-0.339 (-0.601, - 0.077)	0.012
Treatment group 7	-0.071 (-0.295, 0.153)	0.532