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Pharmacokinetics and optimal exposure of antifungal drugs in critically ill patients

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Chapter 4

Subtherapeutic posaconazole exposure and the relation with treatment outcome in patients at risk of and with invasive fungal disease

Abstract

Background: *The posaconazole exposure appears to be subtherapeutic in a part of the patients with invasive fungal disease. Due to the pharmacokinetic variability of posaconazole, therapeutic drug monitoring may help to optimize the efficacy of the antifungal treatment.*

Materials & Methods: *A retrospective study of patients treated with posaconazole from January 2008 to April 2014 and for whom posaconazole serum concentrations were available was conducted. Risk factors for underexposure of posaconazole were detected and the relation between the posaconazole exposure and the treatment outcome according to the EORTC criteria was assessed.*

Results: *Seventy patients met the inclusion criteria, 45 patients received posaconazole as treatment and 25 patients received posaconazole as prophylaxis. The posaconazole serum concentration was < 1.25 mg/L in 44.4% of the patients receiving treatment and < 0.7 mg/L in 40.0% of the patients receiving prophylaxis. Multiple linear regression analysis showed a significant, independent, and negative association of the posaconazole serum trough concentration with a lack of enteral nutrition (P < 0.001), vomiting (P = 0.035), the use of a proton-pump inhibitor or H_2-receptor antagonist (P < 0.001), a liquid diet (P = 0.002), concomitant chemotherapy (P = 0.004), and a posaconazole dose frequency of 2 times daily (P = 0.015). A higher posaconazole concentration was associated with a better treatment outcome (odds ratio = 22.22 [95% confidence interval, 3.40-145.33]; P = 0.001).*

Conclusions: *The posaconazole exposure is not sufficient in over 40% of the patients at risk of or with invasive fungal disease and the posaconazole exposure is positively correlated with a successful treatment outcome. Therapeutic drug monitoring of posaconazole can detect underexposure and can be helpful in treatment optimization.*

4.1   Introduction

Invasive aspergillosis (IA) is the leading cause of infection-related death in patients with acute leukemia and in hematopoietic stem cell transplant (HSCT) recipients [1]. Risk factors for IA are prolonged neutropenia, immunosuppression after stem cell or solid organ transplantation, AIDS, chronic granulomatous disease, and pre-existing structural lung disease [1, 2]. A crude mortality up to 49% is seen and IA is associated with an increase in length of hospital stay and increased costs [2–5]. The guideline of the Infectious Diseases Society of America for the treatment of aspergillosis recommends the use of posaconazole for prophylaxis against IA in neutropenic patients with acute myelogenous leukemia or myelodysplastic syndrome and in HSCT recipients, and as an alternative choice for salvage therapy of IA [2]. The recommended posaconazole dose is 200 mg 3 times daily for prophylaxis and 200 mg 4 times daily for the treatment of IA [6].

Various pathophysiological changes in severely ill patients, such as cancer patients, can affect the pharmacokinetics of antimicrobial agents [7, 8]. Furthermore, drug absorption issues (food, gastric pH) and drug-drug interactions contribute to the intra- and interindividual patient variability of the pharmacokinetics of posaconazole [2, 9–15]. Data from earlier studies with posaconazole showed that average steady state concentrations of at least 0.7 mg/L for prophylaxis and 1.25 mg/L for treatment were associated with a better outcome [16–18]. However, these target concentrations are not attained in a high proportion of patients with hematologic malignancies, resulting in suboptimal drug exposure [19–22]. Therapeutic drug monitoring (TDM) of posaconazole may play an important role in optimizing drug exposure and hence the efficacy of the antifungal treatment [2, 23]. The purpose of this study was to determine risk factors for underexposure of posaconazole and to assess the relation between the posaconazole exposure and the treatment outcome in patients with invasive fungal disease (IFD).

4.2   Materials and methods

4.2.1   Study design and data collection

This retrospective study was conducted at the University Medical Center Groningen, a 1339-bed university hospital in the Netherlands. TDM of antimicrobial drugs is routinely performed in critically ill patients in our hospital. Patients were eligible for inclusion if the following criteria were met: (1) age $\geq$ 17 years, (2) admission between 1 January 2008 and 31 March 2014, (3) treatment with posaconazole, and (4) at least one steady state serum trough concentration of posaconazole available (at least 7 days after the start of the posaconazole treatment and at least 7 days on the same

dose regimen). The study was evaluated by the local ethics committee (Institutional Review Board protocol no. 2013-491) and was approved in accordance with Dutch legislation due to its retrospective nature.

Data were collected through review of the medical records using a standardized case report form. Demographic and clinical data were collected including age, sex, body mass index (BMI), underlying condition, leukocyte count, C-reactive protein (CRP), hepatic function (γ-GT, ALAT, bilirubin, and albumin concentration), presence of a HSCT, vomiting (scored positive if present for ≥ 2 days), diarrhea (for ≥ 2 days), chemotherapy during treatment with posaconazole, and the food intake of the patient. Furthermore, it was determined whether posaconazole was used for prophylaxis or salvage treatment. In case posaconazole was used as treatment, the IFD was classified as proven, probable, or possible according to the 2008 definition of IFD from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group [24]. Besides, data were collected on the posaconazole dose and frequency per day, route of administration (oral/nasogastric tube), posaconazole serum trough concentration, duration of posaconazole treatment, and interacting comedication.

4.2.2   Posaconazole exposure

To evaluate the exposure, posaconazole serum trough concentrations were determined using a validated liquid chromatography-tandem mass spectrometry assay [25] and externally confirmed by proficiency testing [26]. A trough concentration of posaconazole ≥ 0.7 mg/L was considered adequate for prophylaxis and a trough concentration ≥ 1.2 mg/L as adequate for the treatment of IFD [16–19]. To determine risk factors for underexposure of posaconazole, we assessed the association of the first posaconazole trough concentration at steady state with factors that could possibly influence the pharmacokinetics of posaconazole, including the patients' age, BMI, hepatic function, and the CRP concentration [6, 27]. Besides, we compared the posaconazole concentration between patient groups with different gender, food intake, posaconazole dosing schedules, the occurrence of vomiting and diarrhea, concomitant treatment with chemotherapy, and the use of interacting comedication (proton-pump inhibitors (PPI), H_2-receptor antagonists, metoclopramide [10, 14, 28]). Finally, we performed a multiple linear regression analysis to assess the relation between the posaconazole concentration and the explanatory variables.

4.2.3 Treatment outcome and treatment optimization strategies

For patients who received posaconazole as prophylaxis, the presence of a breakthrough fungal infection was noted. For patients who received posaconazole as curative treatment, the outcome was classified as complete, partial, or stable response, progression of the disease, or death, according to the 2008 definition of responses to therapy and study outcomes in clinical trials of IFD from the MSC and EORTC Consensus Criteria [29], at the end of treatment. A complete or partial response was defined as a successful treatment and progression of the disease or death as treatment failure. An ordinal regression analysis was performed to assess the relation between the posaconazole exposure and the treatment outcome (with (1) successful treatment, (2) stable treatment, and (3) treatment failure) correcting for variables that may influence the treatment outcome, including the age and the immune status of the patient.

In patients with a subtherapeutic posaconazole concentration, we evaluated several strategies that were applied to increase the posaconazole concentration: (1) administration of posaconazole with an acidic beverage, (2) discontinuation of the PPI/H_2-receptor antagonist, (3) discontinuation of total parenteral nutrition (TPN) and start administering posaconazole with food, and (4) increase of the posaconazole dose.

4.2.4 Statistical analysis

For the univariate analysis, a Spearman correlation coefficient was calculated to determine correlations between two continuous variables. For comparing 2 or more groups, the Mann-Whitney U test and Kruskal-Wallis test were used. To assess the relationship between the posaconazole exposure and several explanatory variables, variables with a P-value of < 0.10 from the univariate analysis and variables that theoretically can influence the posaconazole exposure were included in the multiple linear regression analysis. Multiple linear regression analysis, with the posaconazole concentration as log-transformed dependent variable, was performed with backward analysis, thereby removing non-significant variables, starting with the one with the highest P value. After performing multiple linear regression, the residuals were checked. For the determination of the relationship of the posaconazole exposure with the treatment outcome in patients receiving curative treatment, an ordinal regression analysis was performed. All statistical analyses were performed using SPSS for Windows, version 22.0 (IBM SPSS, Chicago, Illinois). A P value < 0.05 was considered statistically significant.

Table 4.1: *Patient characteristics (n=70) and indication for antifungal therapy with posacona-
zole. Abbreviations: BMI, body mass index; IFD, invasive fungal disease; IQR, interquartile
range.*

Characteristic	No. of patients (%)
Gender (male)	43 (61.4%)
Age (years, median, IQR)	51 (38-59)
BMI (kg/m^2, median, IQR)	23.4 (21.1-26.8)
Underlying condition	
Hematological malignancies	55 (78.6%)
Acute myeloid leukemia	23 (32.9%)
Acute lymphoblastic leukemia	9 (12.9%)
Non-Hodgkin lymphoma	6 (8.6%)
Hodgkin lymphoma	1 (1.4%)
Chronic myelogenous leukemia	3 (4.3%)
Chronic lymphocytic leukemia	4 (5.7%)
Multiple myeloma	3 (4.3%)
Myelodysplastic syndrome	6 (8.6%)
Solid organ transplantation[a]	8 (11.4%)
Other underlying condition[b]	7 (10.0%)
Posaconazole prophylaxis	25 (35.7%)
Posaconazole treatment	45 (64.3%)
Proven IFD	22 (31.4%)
Aspergillus fumigatus	11 (15.7%)
Aspergillus flavus	1 (1.4%)
Candida non-albicans	3 (4.3%)
Scedosporium[c]	2 (2.9%)
Rhizomucor[d]	2 (2.9%)
Absidia corymbifera	2 (2.9%)
Hormographiella aspergillata	1 (1.4%)
Probable IFD	7 (10.0%)
Possible IFD	16 (22.9%)

[a] *5 patients lung transplantation, 3 patients liver transplantation.*
[b] *1 Cystic fibrosis, 1 HIV, 1 aplastic anemia, 1 myelofibrosis, 1 hemoptysis, 1 thorax trauma, 1
common variable immunodeficiency.*
[c] *1 Scedosporium prolificans, 1 Scedosporium apiospermum.*
[d] *1 Rhizomucor pusillus, 1 Rhizomucor not specified.*

4.3   Results

A total of 81 patients received posaconazole. In 11 patients, TDM of posacona-
zole was not performed or trough samples were obtained before steady state was
reached and they were excluded from the analysis. As a result, 70 patients met the
inclusion criteria and their medical records were reviewed. The median age of the
patients was 51 years (interquartile range [IQR], 38-59 years), and the most com-
mon underlying condition was a hematologic malignancy (78.6%). The patients'
characteristics are summarized in Table 4.1. Twenty-eight patients (40.0%) received
a HSCT, and 22 patients (31.4%) received chemotherapy during treatment with po-
saconazole. Six patients (8.6%) received TPN, 17 patients (24.3%) had a nasogas-
tric tube or a liquid diet, and 47 patients (67.1%) had a normal diet. Twenty-five
patients (35.7%) received posaconazole for prophylaxis, and 45 patients (64.3%) re-
ceived posaconazole as treatment (Table 4.1). In patients receiving posaconazole for
prophylaxis, the posaconazole dose was 600 mg/day in 21 patients (84.0%) and 800
mg/day in 4 patients (16.0%). The median posaconazole serum concentration was
0.9 mg/L (IQR, 0.5-1.7 mg/L) and in 15 patients (60.0%) an adequate posaconazole
trough concentration of ≥ 0.7 mg/L was achieved. For the patients in the treatment
group, the posaconazole dose was 800 mg/day in 36 patients (80.0%), 600 mg/day
in 8 patients (17.8%), and 1 patient received a dose of 960 mg/day. The median po-
saconazole serum concentration was 1.2 mg/L (IQR, 0.6-1.6 mg/L) and 25 patients
(55.6%) had an adequate posaconazole trough concentration of ≥ 1.2 mg/L. Over-
all, 30 patients (42.9%) received interacting comedication with a PPI/H_2-receptor
antagonist, 7 patients (10.0%) received metoclopramide, 1 patient (1.4%) received
rifampicin, and 1 patient (1.4%) received fosamprenavir. The median duration of
treatment with posaconazole was 60 days (IQR, 26-103 days).

4.3.1   Posaconazole exposure

Univariate analysis showed a significant correlation of the posaconazole con-
centration with the albumin concentration (correlation coefficient 0.309; P = 0.014).
The median posaconazole concentration was significantly lower in patients suffer-
ing from vomiting or diarrhea, patients who received concomitant chemotherapy,
and in patients who received a PPI/H_2-receptor antagonist (Table 4.2). Further-
more, the posaconazole concentration was significantly different in patients with a
different food intake. The median posaconazole concentration was 0.3 mg/L (IQR,
0.2-0.3 mg/L) in patients with a lack of enteral nutrition (and receiving TPN), 0.8
mg/L (IQR, 0.4-1.3 mg/L) in patients who had a nasogastric tube or a liquid diet,
and 1.3 mg/L (IQR, 0.8-2.1 mg/L) in patients with a normal diet (P < 0.001). The
median posaconazole concentration was similar in patients with different posaco-

nazole dosing schedules, 1.0 mg/L (IQR, 0.6-1.7 mg/L) for 200 mg 3 times daily, 1.3 mg/L (IQR, 0.6-1.8 mg/L) for 200 mg 4 times daily, and 1.0 mg/L (IQR, 0.4-1.5 mg/L) for 400 mg 2 times daily (P = 0.780), in the univariate analysis. In the multiple linear regression analysis, variables obtained by the univariate analysis (albumin concentration, vomiting, diarrhea, chemotherapy, the use of a PPI/H_2-receptor antagonist, and food intake) and the posaconazole dose were included. The assumptions for linear regression were met, the residuals of the log-transformed posaconazole trough concentration did not deviate from normality and the variance of the residuals was considered homogeneous. The multiple linear regression analysis showed a significant, independent, and negative association of the posaconazole trough concentration with a lack of enteral nutrition (and receiving TPN), vomiting, the use of a PPI/H_2-receptor antagonist, a liquid diet, concomitant chemotherapy, and a posaconazole dose of 400 mg 2 times daily (Table 4.3).

Table 4.2: *Posaconazole concentration between patient groups. Posaconazole trough concentration expressed as median with interquartile range. Abbreviations: PPI, proton pump inhibitor.*

Characteristic	Posaconazole concentration (mg/L)		P value[a]
	Yes	*No*	
Gender (male)	1.0 (0.6-1.4)	1.2 (0.5-2.1)	0.461
Vomitting	0.3 (0.1-0.7)	1.2 (0.6-1.7)	0.006
Diarrhea	0.6 (0.4-1.1)	1.3 (0.6-2.1)	0.008
Chemotherapy	0.9 (0.4-1.4)	1.2 (0.6-2.1)	0.088
PPI / H_2-antagonist	0.6 (0.3-1.1)	1.4 (0.8-2.2)	< 0.001
Metoclopramide	0.9 (0.3-1.4)	1.1 (0.6-1.7)	0.444

[a] *Determined by using the Mann-Whitney U test.*

4.3.2 Treatment outcome and treatment optimization strategies

Of the 25 patients who received posaconazole for prophylaxis, 1 patient (4.0%) had a breakthrough infection with a *Rhizomucor* species resistant to posaconazole. Of the 45 patients who received posaconazole for the treatment of an IFD (age: range 17-75 years), the outcome was classified as a complete response in 24 patients (53.3%) and as a partial response in 8 patients (17.8%). A stable response was seen in 6 patients (13.3%), progression of the disease was seen in 4 patients (8.9%), and 3 patients (6.7%) died during treatment with posaconazole. The median posaconazole concentration was 1.4 mg/L (IQR, 0.8-2.1 mg/L) in patients with a successful treat-

Table 4.3: *Multiple linear regression model of factors significantly associated with the posaconazole concentration. Abbreviations: CI, confidence interval; PPI, proton pump inhibitor. R^2 of the model = 0.562, R^2 change = –0.014, compared with the model with all variables included.*

Factor	Effect	95% CI	P value
Lack of enteral nutrition	–1.140	–1.741 to –0.539	< 0.001
Vomiting	–0.866	–1.671 to –0.061	0.035
PPI / H_2-antagonist	–0.627	–0.923 to –0.331	< 0.001
Nasogastric tube / liquid diet	–0.512	–0.829 to –0.195	0.002
Concomitant chemotherapy	–0.453	–0.758 to –0.147	0.004
Posaconazol frequency 2 times daily	–0.405	–0.727 to –0.083	0.015

ment (complete or partial response), 1.0 mg/L (IQR, 0.5-1.2 mg/L) in patients with a stable response, and 0.3 mg/L (IQR, 0.2-1.3 mg/L) in patients with treatment failure (fungal disease progression or death) (P = 0.010). The ordinal regression analysis showed a significant association of the posaconazole trough concentration with the treatment outcome, when corrected for the age of the patient and the time to recovery of leukocytes. A higher posaconazole concentration (P = 0.001) and a lower age of the patient (P = 0.005) were associated with a better treatment outcome, whereas recovery of leukocytes was not associated with the outcome (Table 4.4).

Table 4.4: *Ordinal regression model of the relationship of the posaconazole exposure with treatment outcome. Abbreviations: CI, confidence interval; OR, odds ratio.*

Factor	OR	95% CI	P value
Posaconazole concentration (mg/L)	22.22	3.40 to 145.33	0.001
Age (years)	0.92	0.86 to 0.97	0.005
Recovery of leukocytes (days)	1.00	0.96 to 1.05	0.841

In 5 patients (20%) in the prophylaxis group and in 8 patients (17.8%) in the treatment group an attempt to increase the posaconazole concentration was performed. In 4 out of 5 patients in the prophylaxis group and in 4 out of 8 patients in the treatment group a therapeutic posaconazole concentration was achieved. Successful strategies were a dose increase (4x 200 mg in the prophylaxis group, 4x 300 mg and 4x 400 mg in the treatment group), discontinuation of the PPI, and the start of enteral nutrition/increasing the food intake. In the other 5 patients, the posacona-

zole concentration remained subtherapeutic after administering posaconazole with an acidic beverage in 3 patients and the discontinuation of a PPI in 2 patients (of which 1 patient had no enteral food intake).

4.4 Discussion

This study showed a subtherapeutic posaconazole concentration in 40% of the patients receiving posaconazole prophylaxis and in 44% of the patients receiving posaconazole treatment. Patients with a higher posaconazole concentration had a better treatment outcome.

Multiple linear regression analysis showed that the posaconazole concentration was significantly associated with the food intake of the patients. Both the lack of enteral nutrition and a liquid diet had a negative effect on the posaconazole concentration, where the effect of no enteral nutrition was most powerful, which was in accordance with earlier findings [11,21,30]. The absorption of posaconazole is significantly increased when posaconazole is administered with a (high-fat) meal [6,30]. When patients are not able to eat or only eat small amounts of a liquid diet, it is not likely that adequate posaconazole concentrations will be reached [30]. Furthermore, co-administration of posaconazole with a PPI or H_2-antagonist had a negative effect on the posaconazole concentration, due to a reduced absorption secondary to a decrease in gastric acid production, and was in agreement with earlier studies [11,12,14,15,31,32]. Administration of the posaconazole oral suspension to patients who are unable to eat or use a PPI/H_2-antagonist should therefore be avoided. The gastro-resistant tablet formulation of posaconazole that recently entered the market [33] or the intravenous formulation [34] that has recently been approved are more suitable for these patients. The posaconazole exposure of the tablet formulation was not reduced when posaconazole was administered with medication affecting gastric pH in healthy volunteers [33]. However, as for the oral suspension, the absorption of posaconazole from the tablet formulation is affected by food, the posaconazole AUC increased by 51% when the tablet was administered with a high-fat meal (compared to a 3- to 4-fold increase with the oral suspension) [35]. For patients suffering from vomiting or who are unable to eat or tolerate oral medication, the intravenous formulation is the most obvious choice. The presence of diarrhea did not show a relation with the posaconazole exposure in the multiple linear regression analysis. Since the oral suspension of posaconazole is predominantly dissolved in the stomach at low pH [30,33], the presence of problems with the intestine is probably less important for the posaconazole absorption. Furthermore, the use of chemotherapy during treatment with posaconazole was negatively associated with the posaconazole exposure. The observed lower posaconazole concentration may be

the result of a reduced absorption due to mucositis, or possibly mucosal dysfunction, villus atrophy, or damaged microbiota [11, 12]. Since posaconazole has a high protein binding of $> 98\%$ [36], and half of the patients with chemotherapy had a low albumin concentration, hypoalbuminemia can lead to an increased volume of distribution and an enhanced clearance of the free drug [8]. Hyper-hydration during chemotherapy is not likely to explain the lower serum concentrations as posaconazole has a large volume of distribution of 7 to 25 L/kg [36]. Finally, the posaconazole concentration was associated with the frequency of posaconazole administration in the multiple linear regression analysis. A dose of 200 mg 4 times a day is recommended in the Summary of Product Characteristics of posaconazole and a dose of 400 mg 2 times a day is suggested as an alternative [6]. Since a dose of 2 times 400 mg gives a lower posaconazole concentration, a more fractionated dose of 4 times 200 mg is a better approach to achieve a sufficient posaconazole exposure. A dose of 2 times daily is possibly an option for patients who receive prolonged courses of posaconazole treatment at home and have a normal food intake and do not use medication that affects gastric pH. A study of Courtney *et al.* demonstrated that the absorption of posaconazole was saturated at a dose of 800 mg [37]. However, this study tested 800 mg as a single dose. Increasing the posaconazole dose to 1200-1600 mg a day in 4 divided doses led to an increased posaconazole trough concentration in 2 patients. This strategy needs to be further studied in patients that receive the oral suspension and have low posaconazole concentrations.

The patients with a successful treatment outcome had a significantly higher posaconazole concentration and there was a positive association of the posaconazole concentration with the treatment outcome. The age of the patient was negatively associated with the treatment outcome. Older patients are likely to be more fragile and have more comorbid medical conditions, which can possibly influence the treatment outcome [38, 39]. We could not demonstrate an effect of the immune status (for the duration of recovery of leukocytes as well as for the actual leukocyte count) of the patients on the treatment outcome. Only a single leukocyte count, obtained at the day of the posaconazole sample, was included in the analysis. The immune status of the patient plays a role in the clearance of the infection; however, the influence of the immune status could not be demonstrated with a single leukocyte count for each patient. When including the duration of the recovery of leukocytes in the analysis, we also could not demonstrate the influence of the immune status on the treatment outcome. Since posaconazole was mainly used as salvage treatment, the leukocytes of most patients already recovered, except for 8 out of 70 patients. Overall response was favorable in 32 patients (71.1%), with a median posaconazole concentration of 1.4 mg/L in this patient group. Our results confirm that the posaconazole target concentration of at least 1.25 mg/L for salvage treatment of IA, which was proposed in

the study of Walsh *et al.*, is associated with a better outcome [16]. Due to the small amount of patients receiving prophylaxis in our study, we cannot make a statement about the proposed target concentration of 0.7 mg/L for prophylaxis.

A limitation of this study is its retrospective nature, although we expect selection bias to be limited since posaconazole concentrations were measured routinely in our hospital. In addition, we used strict criteria for completeness of the data for analysis and we used the EORTC criteria for the evaluation of the treatment outcome. Due to the retrospective nature of this study, we could not score the grade of the mucositis, since this was not routinely scored. We therefore used the presence of diarrhea and chemotherapy during treatment with posaconazole as surrogate markers. Furthermore, we used the first steady state trough concentration of posaconazole for the analysis. However, these concentrations were representative for the whole treatment course since we visually observed that posaconazole concentrations were stable over time.

Since a large proportion of the patients had a low posaconazole exposure and the exposure was associated with the treatment outcome, we believe that TDM has added value for the treatment with posaconazole. Posaconazole was used as salvage treatment in our hospital, which explains the large number of proven cases of IA and the high number of non-*Aspergillus* infections. In case posaconazole is used as salvage therapy for IA, with only few other alternatives left, or when posaconazole is used as treatment for specific and life threatening IFD, for example caused by the class of *Zygomycetes* [40, 41], maximizing the posaconazole exposure is warranted and important for survival. We showed that a favorable outcome can be achieved in salvage therapy with posaconazole in patients with higher posaconazole concentrations. Besides, posaconazole has been associated with an improved safety profile compared to voriconazole and concentration-dependent adverse events have not been identified to date [42]. With the new tablet and intravenous formulation, posaconazole is also suitable for patients with no food intake, absorption problems, and the use of concomitant medication that affects gastric pH. Since the tablet cannot be crushed or chewed, the oral suspension will remain a treatment option for patients who are unable to take tablets, such as patients with dysphagia, which is present in 16 to 23% of the general population [43, 44] and in up to 51% of critically ill patients [45]. The posaconazole oral suspension can also be used in patients with a nasogastric tube, however, the posaconazole absorption is reduced in these patients and TDM is therefore recommended to ensure sufficient posaconazole exposure. The different posaconazole formulations in combination with TDM can help to ensure sufficient posaconazole exposure and assure the efficacy of the antifungal treatment. A prospective randomized clinical trial should be carried out to determine if therapeutic interventions, to increase the posaconazole exposure, result in

an improved treatment outcome.

4.5   Conclusion

The posaconazole exposure was not sufficient in over 40% of patients at risk of or with IFD and was negatively correlated with the lack of enteral nutrition, vomiting, the use of a PPI/H_2-receptor antagonist, a liquid diet, chemotherapy, and a posaconazole dose frequency of 2 times daily. A higher posaconazole concentration was positively associated with a better treatment outcome. Therapeutic drug monitoring of posaconazole can detect underexposure in patients at risk of and with IFD and can be helpful in treatment optimization.

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