Pharmacokinetics of antifungal drugs in severely ill patients

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CHAPTER 6

Inflammation is associated with voriconazole trough concentrations

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ABSTRACT

Voriconazole concentrations display a large variability, which cannot completely be explained by known factors. Inflammation may be a contributing factor, as inflammatory stimuli can change the activities and expression levels of cytochrome P450 isoenzymes.

We explored the correlation between inflammation, reflected by C- reactive protein (CRP) concentrations, and voriconazole trough concentrations. A retrospective chart review of patients with at least one steady-state voriconazole trough concentration and a CRP concentration measured on the same day was performed. A total of 128 patients were included. A significantly ($P < 0.001$) higher voriconazole trough concentration was observed in patients with severe inflammation (6.2 mg/L; interquartile range [IQR], 3.4 to 8.7 mg/L; n=20) than in patients with moderate inflammation (3.4 mg/L; IQR, 1.6 to 5.4 mg/L; n=60) and in patients with no to mild inflammation (1.6 mg/L; IQR, 0.8 to 3.0 mg/L; n=48). The patients in all three groups received similar voriconazole doses based on mg/kg bodyweight ($P = 0.368$). Linear regression analyses, both unadjusted and adjusted for covariates of gender, age, dose, route of administration, liver enzymes, and interacting coadministered medications, showed a significant association between voriconazole and CRP concentration ($P < 0.001$). For every 1-mg/L increase in the CRP concentration, the voriconazole trough concentration increased by 0.015 (unadjusted 95% confidence interval [CI], 0.011 to 0.020 mg/L; adjusted 95% CI, 0.011 to 0.019 mg/L). Inflammation, reflected by the C-reactive protein concentration, is associated with voriconazole trough concentrations. Further research is necessary to assess if taking the inflammatory status of a patient into account is helpful in therapeutic drug monitoring of voriconazole to maintain concentrations in the therapeutic window, thereby possibly preventing suboptimal treatment or adverse events.

INTRODUCTION

Voriconazole, a broad-spectrum antifungal agent, is considered a first-line agent for the treatment of invasive aspergillosis (1). Several studies showed a relation between the efficacy and safety of voriconazole and voriconazole trough concentrations (2-7). Voriconazole trough concentrations of >1.5 mg/L are associated with a favorable response to treatment. High voriconazole trough concentrations are associated with an increased incidence of adverse events, such as visual disturbances, hallucinations and abnormalities in liver enzymes levels. The Infectious Diseases Society of America guidelines recommend determination of voriconazole concentrations in conjunction with other measures of clinical assessment to evaluate potential toxicity or to document adequate voriconazole exposure (1).

In daily practice, a large variability in voriconazole concentrations is observed, not only between patients (8) but also within individual patients over time (9). Polymorphisms of cytochrome P450 isoenzymes (10), impaired liver function (11), and drug-drug interactions (12) influence voriconazole pharmacokinetics but do not completely explain the observed variability. Therefore, other factors may contribute to the variability of voriconazole pharmacokinetics.

We expect that inflammation could be one of these factors. Infections or inflammatory stimuli can change the activities and expression levels of various forms of cytochrome P450 isoenzymes (13). The downregulation of cytochrome P450 isoenzymes during inflammation decreases the hepatic clearance of drugs that are metabolized by these enzymes. As voriconazole is extensively metabolized by cytochrome P450 isoenzymes 2C19, 3A4, and 2C9 (14), inflammation may contribute to the variability of the pharmacokinetics of voriconazole.

The aim of this retrospective study was to investigate whether inflammation, reflected by C-reactive protein (CRP) concentrations, is associated with voriconazole trough concentrations.

PATIENTS AND METHODS

A retrospective chart review was performed for all patients aged ≥ 18 years who had at least one steady-state voriconazole trough concentration and a CRP concentration

measured on the same day. The patients were treated at the University Medical Center Groningen, The Netherlands, between January 2006 and December 2010. Patients who were concomitantly using a strong inhibitor or inducer of cytochrome P450 isoenzymes were excluded. Steady state was considered to be achieved after 6 doses when 2 loading doses were administered (15), after 10 doses when <2 loading doses were administered (16), and 6 doses after a dosage adjustment (17). We measured voriconazole serum concentrations using a validated method that involved liquid chromatography coupled with tandem-mass spectrometry (18). This study was evaluated by the local ethics committee (IRB 2013-491) and was in accordance with the Dutch law because of its retrospective nature.

For each eligible patient, data that included demographic details, medical history, and laboratory parameters were collected from the medical chart. In addition to the voriconazole trough and CRP concentrations, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (γGT), and total bilirubin concentrations were collected. Information on voriconazole treatment was also gathered. In addition, we evaluated medication used concomitantly that may have influenced the voriconazole concentrations by means of interactions with cytochrome P450 isoenzymes 2C19 and 3A4.

Numerical variables are summarized as medians and interquartile ranges (IQRs), and categorical variables are summarized as frequencies and percentages.

To explore the possible association of inflammation with voriconazole trough concentrations, voriconazole trough concentrations of patients with no to mild inflammation (CRP, ≤40 mg/L), those with moderate inflammation (CRP, 41 to 200 mg/L), and those with severe inflammation (CRP, >200 mg/L) (19, 20) were compared using a Kruskal-Wallis test. A linear regression analysis was performed to assess the contribution of inflammation, reflected by CRP concentrations, to the variability in voriconazole trough concentrations, both unadjusted and adjusted for gender, age, dose, route of administration, alkaline phosphatase, ALT, AST, γGT, total bilirubin, and interacting comedication covariates. We corrected for these variables as much as possible to determine the direct association of inflammation (reflected by CRP concentrations) with voriconazole trough concentrations. For each patient, only the first steady-state voriconazole trough concentration with a CRP

concentration measured on the same day was used for analysis. These analyses were performed using IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Based on data from the hospital information system, we selected patients who had a steady-state voriconazole trough concentration and a CRP concentration measured on the same day. Of these 133 patients, 128 patients were included in our analysis. Five patients were excluded because they concomitantly used phenytoin (n=2), rifampicin (n=2), or HIV medication (n=1).

The patient characteristics are shown in Table 1. The median values of most laboratory parameters were inside their respective normal ranges. CRP and γGT concentrations were higher than the upper limit of normal. Regarding medication used concomitantly, which potentially influenced voriconazole concentrations, only omeprazole and esomeprazole were used simultaneously with voriconazole.

A significantly ($P < 0.001$) higher voriconazole trough concentration was observed in patients with severe inflammation (6.2 [IQR, 3.4 to 8.7] mg/L; n=20) than in patients with moderate inflammation (3.4 [1.6-5.4] mg/L; n=60) and no to mild inflammation (1.6 [0.8-3.0] mg/L; n=48). These differences are shown in Fig. 1. The patients in all three groups received similar doses of voriconazole ($P = 0.368$) twice daily. The median (IQR) voriconazole doses were 3.0 (2.5 to 3.8) mg/L for patients with no to mild inflammation, 3.6 (2.7 to 3.9) mg/L for patients with moderate inflammation, and 3.5 (2.9 to 4.0) mg/L for patients with severe inflammation. Of the 48 patients with a CRP of ≤40mg/L, only one patient (2.1%) had a voriconazole trough concentration of >5 mg/L (5.8 mg/L). Of the 20 patients with a CRP concentration of >200 mg/L, none had a voriconazole trough concentration of <1.5 mg/L.

TABLE 1 Patient characteristics[a]

Characteristic	No. (%) of patients or median (IQR)
Demographic	
Gender (female)	59 (46)
Age (yr)	55 (42-62)
Weight (kg)	75 (61-85)
Height (m)	1.75 (1.67 - 1.81)
BMI[b] (kg/m^2)	24.2 (21.6 - 26.6)
Underlying disease	
Hematologic malignancy	67 (52)
Solid organ transplant	34 (27)
Other[c]	27 (21)
Voriconazole treatment	
Twice-daily dose (mg/kg)	3.3 (2.6-3.9)
Intravenous administration	64 (50)
Laboratory parameter	
Voriconazole (mg/L)	2.7 (1.3-4.8)
CRP (mg/L	71 (15-152)
Alkaline phosphatase (U/L)	114 (71-192)
ALT (U/L)	36 (17-69)
AST (U/L)	31 (19-61)
γ- glutamyl transferase (U/L)	105 (55-232)
Total bilirubin (μmol/L)	9 (6-16)
Coadministered medication	
(Es)omeprazole	81 (63)

[a] n = 128.
[b] BMI, body mass index.
[c] Other diagnosed diseases included chronic pulmonary obstructive disease, cystic fibrosis, and granulomatosis with polyangiitis

The association between CRP concentrations and voriconazole trough concentrations was significant in both the unadjusted ($P = < 0.001$) and adjusted linear regression analyses ($P = < 0.001$). For every 1-mg/L increase in the CRP concentration, the voriconazole trough concentration increased by 0.015 mg/L in each of the two analyses (unadjusted 95% confidence interval [CI], 0.011 to 0.020; adjusted 95% CI, 0.011 to 0.019). The adjusted linear regression analysis explained 46% of the variance in voriconazole trough concentration. Figure 2 shows the voriconazole and CRP concentrations of a patient during treatment with voriconazole.

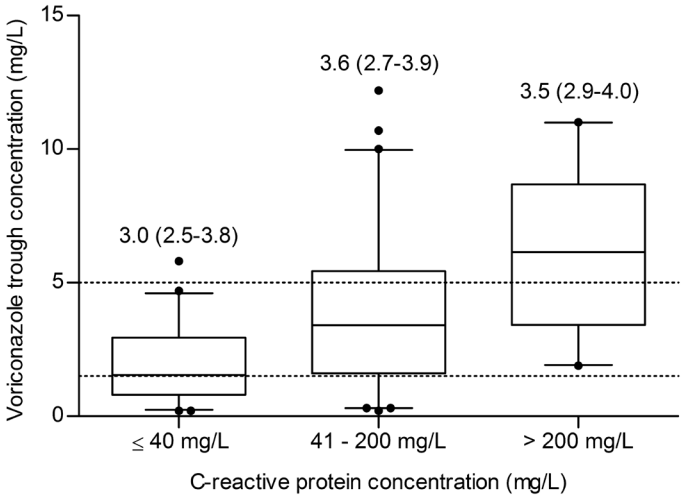

FIG 1 Box (median and 25th to 75th percentile) and whisker (5th and 95th percentile) plots of voriconazole trough concentrations for patients with no to mild inflammation (n = 48), moderate inflammation (n = 60), and severe inflammation (n = 20). The filled circles represent outliers. The median (interquartile range [IQR]) voriconazole dose (in mg/kg of body weight) for each group is displayed above each box-and-whisker plot. The dotted lines represent the therapeutic window of voriconazole trough concentrations.

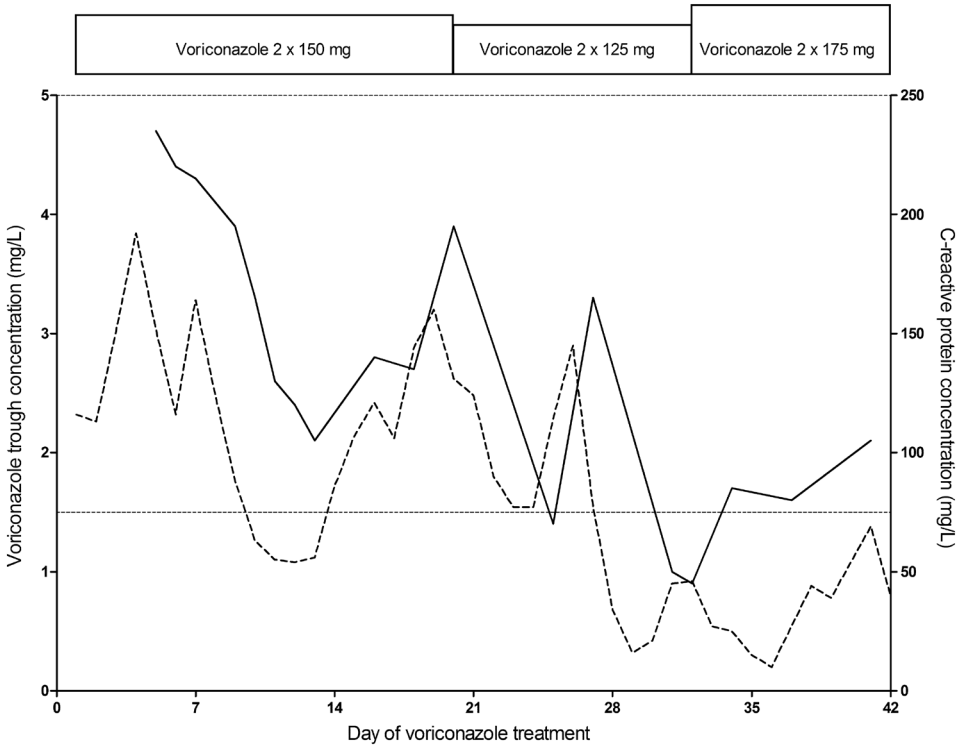

FIG 2 Voriconazole trough concentrations (solid curve) and CRP concentrations (dashed curve) of a 46-year-old male patient with cystic fibrosis who was admitted to the intensive care with respiratory insufficiency and was treated with voriconazole after *Aspergillus fumigatus* was isolated from his respiratory secretions. On day 24, the patient received a bilateral lung transplant. The dotted lines represent the therapeutic window of voriconazole.

DISCUSSION

This is the first study to show that inflammation, reflected by C-reactive protein concentration, is associated with voriconazole trough concentrations. The multiple linear regression analysis showed that, for every 1-mg/L increase in CRP concentration, the voriconazole trough concentration was 0.015 mg/L higher. These results provide a possible explanation for some of the variability of voriconazole concentrations.

Inflammation is associated with the variability observed between and within patients at different time points, regardless of polymorphisms of cytochrome P450

isoenzymes (10), impaired liver function (11), and drug-drug interactions (12), which are already known to influence voriconazole pharmacokinetics. The inflammatory status of patients is different and can change over time during voriconazole treatment, which alters inflammatory cytokine concentrations. The inflammatory cytokines cause a downregulation of cytochrome P450 isoenzymes at the level of gene transcription, which results in a decrease in the corresponding mRNA, protein, and enzyme activities (13, 21-23). These decreases change the rate of the metabolism of voriconazole, resulting in variable voriconazole concentrations. Trifilio et al. hypothesized that the observed variability is caused by multiple factors, including changes in absorption, patient protein status, liver function, and disease modifying effects, such as graft versus host disease (9). Long-term exposure to voriconazole has been suggested to cause auto-induction of cytochrome P450 isoenzymes, resulting in decreasing voriconazole concentrations (24). However, autoinduction has not been seen in healthy human volunteers (25).

A limitation of this study is its retrospective nature, which possibly introduced selection bias and limited the availability of desired data. The impact of selection bias on the results was expected to be limited, given that voriconazole concentrations were measured in most patients in our hospital, not only when efficacy or safety was in question. Information on the genetic polymorphisms of the cytochrome P450 isoenzymes in individual patients was not available, because these were not determined in routine patient care. Therefore, we could explain only a part of the variability of voriconazole pharmacokinetics. Cytochrome P450 polymorphisms contribute to the variability of voriconazole pharmacokinetics between patients (10). Polymorphisms might explain some of the pharmacokinetic variability of voriconazole, in particular the unexplained variability in our model. It is unlikely that polymorphisms completely explain the observed variability, because the prevalence of poor metabolizers of CYP2C19, who likely contribute most to the variability of voriconazole trough concentrations between patients, is only 3 to 5% in the Caucasian population (26).

CRP concentrations were used as markers for inflammatory status because the concentrations of inflammatory cytokines were not available in this retrospective study. Cytokines stimulate the production of acute-phase proteins; CRP concentrations in particular change rapidly when the inflammatory status of a

patient changes (27). As a result, CRP concentrations are used extensively in daily practice as markers for inflammation.

Further research that includes information about cytochrome P450 isoenzyme polymorphisms is necessary. We suggest a prospective study to investigate if a dosing algorithm can be developed to predict the voriconazole concentration on the basis of patient characteristics and voriconazole dose and route of administration.

In conclusion, we have shown that inflammation, reflected by the CRP concentration, is associated with voriconazole trough concentrations. Further research is necessary to assess if accounting for the inflammatory status of a patient is helpful in therapeutic drug monitoring of voriconazole to maintain concentrations in the therapeutic window, thereby possibly preventing suboptimal treatment or adverse events.

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