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Influence of Inflammation on Voriconazole Metabolism

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Voriconazole pharmacokinetics shows a large inter- and intrapatient variability. Inflammation is associated with changes in the expression of CYP isoenzymes. Here, we evaluated the influence of inflammation, marked by C-reactive protein (CRP) levels in blood, on the metabolism of voriconazole. Observational data showed an association between CRP level and the ratio of voriconazole *N*-oxide to voriconazole.

Voriconazole (VCZ) is recommended as a first-line treatment for invasive aspergillosis (1). It undergoes extensive hepatic metabolism, primarily by CYP2C19 and to a lesser extent by CYP3A4 and CYP2C9. Besides polymorphism as a predominant factor generating highly variable interpatient pharmacokinetics of VCZ, drug-drug interactions and liver function may also influence VCZ exposure (2–4). A recent observation of high VCZ concentrations during severe inflammation (5) could explain a part of the previously observed large intrapatient variability (6). This effect was explained by a downregulation of drug-metabolizing enzymes caused by inflammation (7, 8).

To further elucidate this clinical observation, it was relevant to evaluate the metabolic rate of VCZ during periods of severe inflammation. The metabolic rate of VCZ was expressed as the ratio of *N*-oxide VCZ to VCZ (metabolic ratio [MR]). In this study, we hypothesize that the *N*-oxide VCZ/VCZ ratio would be decreased during severe inflammation (defined by C-reactive protein [CRP] levels of >100 mg/ml), possibly due to a decrease in the metabolic function of CYP2C19.

In this study, performed in the University Medical Centre Groningen, the Netherlands, medical data from patients who received intravenous or oral VCZ for treatment or prophylaxis between December 2012 and July 2013 and were subjected to therapeutic-drug monitoring (TDM) and monitoring of CRP were retrospectively analyzed. All patients aged at least 18 years who received VCZ were considered eligible for the study if they had at least 3 data sets of *N*-oxide VCZ/VCZ concentration ratios and corresponding CRP levels determined on the same day. This study, being of a retrospective nature, was evaluated by the local ethics committee (IRB 2013-491) and was approved according to Dutch law.

Patients were excluded if a strong cytochrome P450 inducer or inhibitor affecting VCZ metabolism was coadministered (4) or if the mean value of liver function tests exceeded 5 times the upper level of normal. The liver functions evaluated were alanine aminotransferase (ALT; normal value, <45 U/liter), aspartate aminotransferase (AST; normal value, <40 U/liter), alkaline phosphatase (AP; normal value, <120 U/liter), and bilirubin (normal value, 5.1 to 32.5 μmol/liter). VCZ and *N*-oxide VCZ concentrations were measured with a validated and verified assay (9, 10). CRP was measured by a turbidimetric assay (Roche Modular; Roche, Mannheim, Germany).

In the study, data for a total of 77 patients who were subjected to routine TDM during the period from December 2012 to July 2013 were evaluated. After the evaluation, 28 patients were eligible for the study because of having a complete data set of VCZ levels and CRP concentration in blood samples taken together on the same day. From this group, 9 patients were excluded because of drug-drug interaction (DDI) ($n = 6$) and liver dysfunction ($n = 3$), and thus, 19 patients remained in the study. The demographic information and descriptive statistics of the selected patients are summarized in Table 1. In total, 101 data sets were available for analysis, ranging from 3 to 21 data sets per patient. The mean metabolic ratio was 2.4, with a 95% confidence interval (CI) of 0.0 to 30.0. The mean plasma concentration of CRP was 76.6 (range, 5.0 to 279.0), that of VCZ was 3.4 mg/liter (range, 0.1 to 12.3), and that of *N*-oxide VCZ was 2.4 mg/liter (range, 0.1 to 8.4).

The association between the MR and CRP levels from all selected patients was analyzed using correlation analysis. Our data confirm that an inflammatory response is significantly positively associated with the VCZ concentration (rho = 0.62; 95% CI, 0.48 to 0.73; $P < 0.001$) and negatively associated with the metabolic ratio (rho = −0.64; 95% CI, −0.77 to −0.50; $P < 0.001$). A comparison of the Pearson (parametric) and Spearman (nonparametric) coefficients of correlation was used to show the normal distribution of the data. An important limitation of the study is that infrequent sampling for VCZ and CRP in routine care made it difficult to detect subtle changes in metabolic clearance. Differences in response rates to antimicrobial treatment affecting inflammation complicated the alignment of the results with respect to time for mixed effects modeling. A linear mixed model analysis (with a random intercept for subjects) was performed to assess the influence of inflammation on the variability in VCZ trough concentrations and MR. VCZ increased with 0.021 mg/liter for unit

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TABLE 1 Demographic and clinical characteristics of patients

Parameter	Result[a] ($n = 19$ patients)
Characteristics	
Female/male	6/13
Age (yr)	57 (IQR, 18–68)
Wt (kg)	63 (IQR, 50–92)
Ht (cm)	171 (IQR, 160–193)
Underlying diseases	
Hematologic malignancy	13
Organ transplant	3
Other	3
Drug administration	
Oral/intravenous (%)	21/48
Transition from i.v. to oral/oral to i.v. (%)	26/5
Dose (mg twice a day)	200 (R, 150–320)
Laboratory findings	
CRP (mg/liter)	76.6 (R, 5.0–279.0)
VCZ (mg/liter)	3.3 (R, 0.1–12.3)
N-oxide VCZ (mg/liter)	2.4 (R, 0.1–8.4)
ALT (U/liter)	93.70 (IQR, 11–107.7)
AST (U/liter)	51.07 (IQR, 8–409)
Alkaline phosphatase (U/liter)	130 (IQR, 47–258)
Total bilirubin (μmol/liter)	9 (IQR, 6–16)

[a] Values are the number, percent, mean (range [R]), or median (interquartile range [IQR]), as indicated.

increase in the CRP level, and MR decreased with a −0.010 for every unit increase in the CRP level ($P < 0.001$ for both results). Liver function tests showed no significant influence on either VCZ or MR. The hypothesis that metabolism of VCZ is reduced during severe inflammation seems plausible, as shown by the significant negative correlation between CRP and the MR. It should be kept in mind that in this study, the heterogeneous population was relatively small due to a lack of available data from routine care. Despite this limitation, inflammation seems to be a relevant source of VCZ pharmacokinetic variability (5), because other major factors, such as DDI and hepatic dysfunction, were a reason to exclude patients. If information on CYP2C19 polymorphisms had been available, it is likely that the pharmacokinetic variability could have been explained even better (11). Due to this lack of information on genetic polymorphism in our study, the difference in the extent of the effect of inflammation on the VCZ concentrations between patients who are poor metabolizers or extensive metabolizers remains to be evaluated. It can be speculated that, in cases of poor metabolism, a dose reduction during inflammation is warranted to avoid toxicity.

Nevertheless, prospective studies with frequent sampling are needed to investigate the true impact of this phenomenon. This could be important not only for VCZ but also for other drugs that are metabolized by CYP2C19. Depending on the therapeutic windows of these drugs, patients may experience side effects during severe inflammation, due to decreased metabolism resulting in high drug plasma concentrations.

The findings in our study are consistent with and confirm the ideas of Morgan and collaborators, who claimed that CYP450-mediated drug metabolism is reduced during severe inflammation (7, 8). Therefore, consideration of the effects of an inflammatory state on the variability in drug response should be an integral part of a personalized treatment. For instance, routine TDM of VCZ in the clinic has been suggested to reduce the number of discontinuations of VCZ treatment due to adverse events and even to improve the success rate in the treatment of invasive fungal infections (12).

In conclusion, this study provides support for the hypothesis that the effect of an inflammatory response on VCZ metabolism is a source of the variability of VCZ plasma concentrations. Our data show that inflammation and infection play a role in the largely unpredictable pharmacokinetics of VCZ. As a consequence, physicians should be aware of this phenomenon in order to avoid inflammation-associated increasing levels of VCZ and, thereby, toxic responses to VCZ.

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