Pharmacokinetics of antifungal drugs in severely ill patients

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CHAPTER 5

Voriconazole therapeutic drug monitoring practices in the intensive care

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ABSTRACT

Routine therapeutic drug monitoring of voriconazole appears to be beneficial. This study investigated the therapeutic drug monitoring practices on the intensive care to derive possible recommendations for improvement. A retrospective chart review was performed for patients aged ≥ 18 years started treatment with voriconazole that lasted for at least three days while admitted to an intensive care unit (ICU) to assess possible differences between the patients with and without voriconazole trough concentrations measured. In 64 (76%) of the 84 patients, voriconazole trough concentrations were measured. The groups differed significantly with respect to the duration of voriconazole treatment and ICU admission. Timing of sampling was premature for 66% of the first measured voriconazole trough concentrations and in 48% of the subsequent measured concentrations. Of the 349 trough concentrations measured, 129 (37%) were outside the therapeutic window. In 11% of these cases no advice was provided without identifiable reason. In addition, 27% of the advised dose adjustments were not implemented, probably because the advice was not suited for the specific clinical situation. The performance of voriconazole therapeutic drug monitoring can still be improved although voriconazole concentrations were monitored in most patients. A multidisciplinary approach - for instance by means of antifungal stewardship will probably be able to overcome problems encountered like timing of sampling, incompleteness of data on clinical context and lack of implementation of recommendations.

INTRODUCTION

Several studies have shown a correlation between the efficacy and safety of voriconazole and voriconazole trough concentrations (1-8). Based on these studies a voriconazole trough concentration above 1.5 mg/L is recommended, as this is associated with a favorable response (4). Voriconazole trough concentrations above 5.0 mg/L should be avoided as these are associated with an increased incidence of adverse events, such as visual disturbances and hallucinations (1).

Therapeutic drug monitoring may be helpful to optimize treatment because of the large inter- and intra-individual variability in voriconazole concentrations (9, 10) and the relation between voriconazole trough concentrations and efficacy and safety. Therefore, the Infectious Diseases Society of America guidelines recommend determination of voriconazole concentrations, in conjunction with clinical assessments to evaluate potential toxicity or to document adequate voriconazole exposure (11). A recent randomized controlled study showed that routine therapeutic drug monitoring of voriconazole may reduce drug discontinuation due to adverse events and improve the treatment response in invasive fungal infections (5). Routine therapeutic drug monitoring of voriconazole could therefore be advocated, especially in critically ill patients since several of the elucidated mechanisms for the pharmacokinetic variability are frequently present in these patients, as impaired liver function (12), drug-drug interactions (13) and inflammation (14). We speculate that voriconazole therapeutic drug monitoring in routine intensive care unit (ICU) practice can be improved.

The aim of this retrospective study was to investigate the routine practice of voriconazole therapeutic drug monitoring on the ICU and derive possible recommendations for improvement.

PATIENTS AND METHODS

A retrospective chart review was performed for all patients aged ≥ 18 years that started treatment with voriconazole while admitted to an intensive care unit in the University Medical Center Groningen, The Netherlands, between January 2007 and December 2012. The patients studied were retrieved from the pharmacy prescription database, since voriconazole was not on stock in the ICU and had to be ordered

in the pharmacy department with identification of the patient. Patients receiving voriconazole for less than three days were excluded. This study was evaluated by the local ethics committee (IRB 2013-491) and was approved in accordance with Dutch legislation due to its retrospective nature.

For each eligible patient, data were collected from the medical chart, including demographic data, medical history and voriconazole trough concentrations. Voriconazole serum concentrations were measured using a validated liquid chromatography tandem-mass spectrometry method (15). Data that were collected from the medical chart were underlying disease, indication for treatment, voriconazole treatment duration on the ICU and duration of the ICU admission, route of administration at the start of treatment, why voriconazole treatment was ended on the ICU and the overall mortality 4 and 12 weeks after the start of voriconazole treatment. Regarding the indication for treatment, a distinction was made between patients with an invasive fungal infection based on either the EORTC/MSG criteria (16) or the clinical algorithm for critically ill patients (17), patients receiving either pre-emptive or empirical treatment and patients receiving prophylaxis with voriconazole.

Possible differences between the patients with and without voriconazole trough concentrations measured were assessed by the Mann-Whitney U test (continuous data) and the Fisher's exact test (categorical data). Numerical variables are summarized with medians and interquartile range and categorical variables are summarized with frequencies and percentages. To explore a possible influence of treatment duration on the number of measured voriconazole trough concentrations, their correlation was assessed with a Spearman correlation coefficient. These analyses were performed using IBM SPSS Statistics 20 (IBM Corp., Armonk, NY, USA).

To gather information about the time of sampling, we examined the moment of the first trough concentration measured, the subsequent voriconazole concentrations and of the last measured concentration on the ICU. The moment of sampling was considered to be premature, adequate or fairly late. For the first measured voriconazole trough concentration timing was considered adequate between day 4 to 7. Subsequently measured voriconazole concentrations were considered adequately timed when drawn 2 to 5 days after the previous sample. For the last measured

voriconazole concentration timing was considered adequate when drawn not more than 5 days before the end of voriconazole treatment on the ICU.

For optimization of voriconazole treatment it is not only important to measure voriconazole trough concentrations adequately (18), but also to provide the clinician with appropriate advice. Therefore we investigated the recommendations based on the corresponding voriconazole trough concentrations that were outside the therapeutic window. In addition we evaluated the subsequent implementation of these recommendations.

For an impression of the course of voriconazole trough concentrations during ICU admission a boxplot was drawn with the trough concentration measured over time. Also, the difference was plotted between the two most extreme voriconazole trough concentrations measured for patients with two or more trough concentrations.

RESULTS

Eighty-four patients with a median age of 55 (IQR: 44 - 63) were included, 55 were males. Patients received voriconazole treatment on the ICU for a median of 10 (6-20) days. Table 1 displays the patient characteristics of the patients with and without voriconazole trough concentrations measured. The groups significantly differ with respect to voriconazole treatment duration on the ICU and the duration of ICU admission. The number of voriconazole trough concentrations measured showed a positive correlation with the voriconazole treatment duration on the ICU ($r_s = 0.721$; $P < 0.001$).

The timing of the measured voriconazole concentrations is illustrated in figure 1. Remarkably, 66% of the first samples were taken before day 4, at which steady-state was expected in patients receiving a loading dose.(19) Almost half (48%) of the subsequent voriconazole trough concentrations were measured prematurely.

TABLE 1 Patient characteristics of patients treated with voriconazole with and measured.

Demographics	With (n=64)	Without (n=20)	*P* value
Male (n=55)	42 (66%)	13 (65%)	1.000
Age (yr)	55 (44-63)	55 (41-64)	0.854
Underlying disease			0.509
Solid organ transplant (n=43)	35 (55%)	8 (40%)	
Hematological malignancy (n = 10)	7 (11%)	3 (15%)	
Other[a] (n=31)	22 (35%)	9 (45%)	
Treatment			0.093
Prophylaxis (n=8)	4 (6%)	4 (20%)	
Pre-emptive/empirical treatment (n=42)	31 (49%)	11 (55%)	
Treatment (n=34)	29 (45%)	5 (25%)	
Duration of voriconazole treatment on ICU (days)	13 (7-23)	6 (3-8)	<0.001
Duration of ICU admission (days)	32 (17-51)	13 (6-22)	<0.001
Intravenous start of voriconazole (n=56)	43 (67%)	13 (65%)	1.000
End of voriconazole treatment			0.459
End of treatment (n=23)	20 (31%)	3 (15%)	
Switch (n=13)	10 (16%)	3 (15%)	
Discharged to ward (n=30)	22 (34%)	8 (40%)	
Deceased (n=18)	12 (19%)	6 (30%)	
Overall mortality			
4 week (n=21)	14 (22%)	7 (35%)	0.250
12 week (n=30)	23 (36%)	7 (35%)	1.000

Data presented as n (%) or median (IQR)

[a] Other: patients diagnosed with various disorders including chronic pulmonary obstructive disease, cystic fibrosis, and collagen-vascular disease.

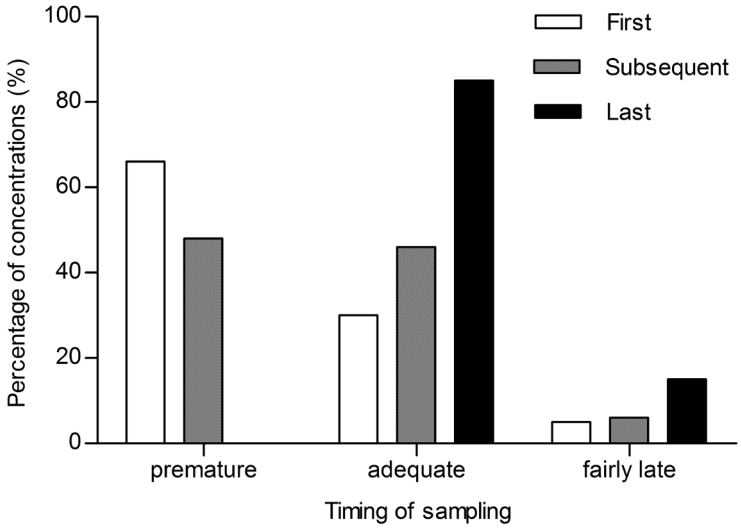

FIG 1 Percentage of voriconazole trough concentrations considered to be timed premature, adequate or fairly late for the first, the subsequent and the last measured voriconazole trough concentrations.

A total of 349 voriconazole trough concentrations were measured, of which 27% were considered subtherapeutic (<1.5 mg/L), 63% were adequate (1.5 – 5.0 mg/L) and 10% were above 5.0 mg/L. A median of 4 (2-8) voriconazole trough concentrations were measured per patient. Figure 2 provides insight in the given advice and the follow-up. In most cases an advice was given by the hospital pharmacist of which in 65% of the cases a dose adjustment was recommended. Lower trough concentrations were accepted in case of prophylaxis or coinciding liver test abnormalities. High trough concentrations were accepted in case of infections in sanctuary sites and in case of last resort. The clinical situation of the patient seemed a reason for the physician for not implementing the advised dose adjustment. Almost half of the voriconazole trough concentrations measured subsequently after an implemented dose adjustment was still outside the therapeutic window. This could partially be explained because 10 (40%) of these samples were drawn the next day.

The voriconazole trough concentrations measured over time are displayed in figure 3. Over time, we noticed a decreasing trend in voriconazole trough concentrations. Figure 4 illustrates the percent change between the two most extreme voriconazole trough concentrations measured in individual patients.

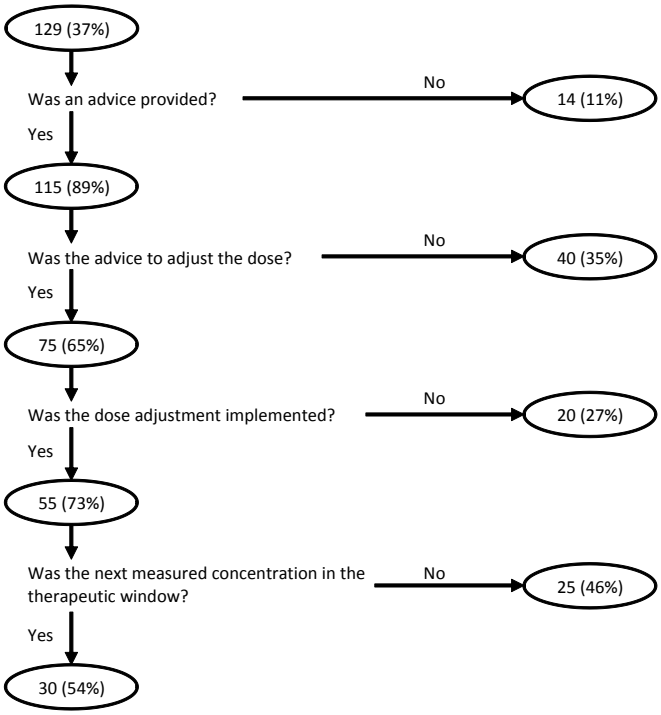

FIG 2 Provided advices and implementation of the advices for voriconazole trough concentrations outside the therapeutic window.

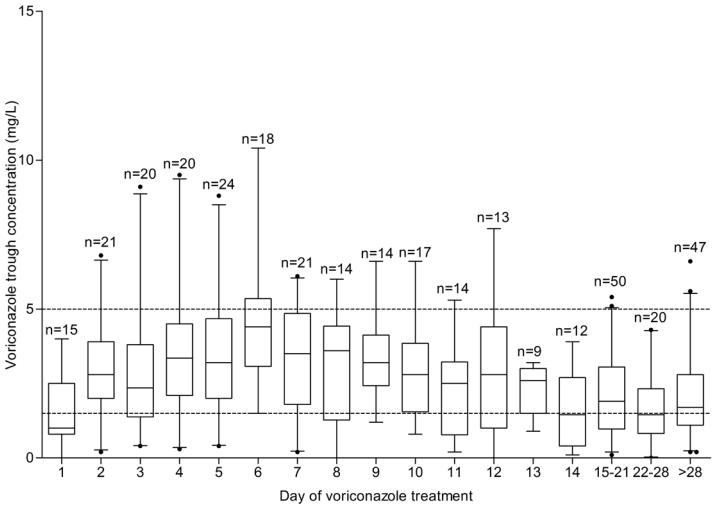

FIG 3 Box (median and 25th to 75th percentile) and whisker (5th and 95th percentile) plots of voriconazole trough concentrations (n = 349) observed over time. Filled circles are outliers; n is the number of concentrations measured on that day of treatment. The dashed lines represent the therapeutic window of voriconazole trough concentrations.

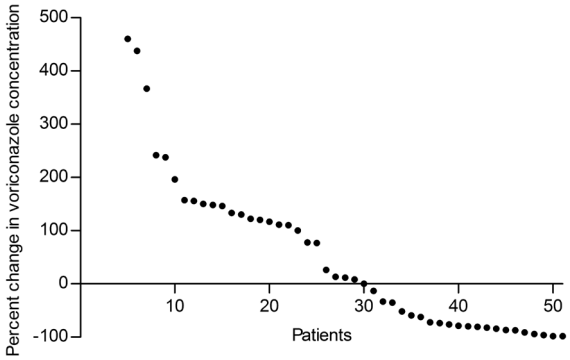

FIG 4 Percent change between the two most extreme voriconazole trough concentrations measured for patients (n = 51) with 2 or more concentration measurements available. Due to constraints of scale the four highest changes (1087, 1433, 3400 and 6500%) were not plotted. Positive numbers represent an increase over time and negative numbers represent a decline.

DISCUSSION

This is the first study that provides information about the daily practice of voriconazole therapeutic drug monitoring in the ICU. Our data confirmed the large inter- and intra-individual variability in voriconazole trough concentrations (9, 10). The results of this study also suggest that there is awareness among the ICU staff regarding the need for therapeutic drug monitoring for voriconazole as in a large proportion of the patients voriconazole trough concentrations were assessed. However several aspects of voriconazole therapeutic drug monitoring need continuous attention since it may help optimize its value in reducing drug discontinuation due to assumed adverse events and improving treatment response (5).

Next to regularly monitoring voriconazole trough concentrations, the timing of sampling is important as well. Premature sampling occurred frequently for both first and subsequent samples. At this moment, sampling before steady state has been reached complicates interpretation of trough concentrations and therefore often additional samples are necessary making therapeutic drug monitoring less efficient. Pharmacokinetic modeling, to enable interpretation of non-steady state concentrations and to enhance the predictability of dose adjustments, is under development (20) but has not yet been implemented in daily practice.

Professionals providing therapeutic drug monitoring services should endeavor

to provide a tailor-made advice for every voriconazole trough concentration outside the therapeutic window even when clinical information is lacking. Our data showed that voriconazole therapeutic drug monitoring would benefit from a multidisciplinary approach in which the measured trough concentration is viewed in relation to the clinical context. Education alone will likely not be sufficient, since the effect of education on health care professionals is limited (21) and wanes with time (21, 22), especially in teaching hospitals due to frequent changes in staff. A more active role of the pharmacist improved vancomycin therapeutic drug monitoring in hospitalized pediatric patients (21). This more active involvement would fit well in the context of antifungal stewardship. Valerio et al. concluded that antifungal stewardship is urgently needed after they observed that the selection and duration of antifungal therapy was substandard (23). We expect that voriconazole therapeutic drug monitoring could as well benefit from antifungal stewardship.

The retrospective nature and its consequent incompleteness of data may be considered as limitations. However, the aim of our study was to investigate the clinical application of therapeutic drug monitoring as several studies already showed the relation between treatment outcome and voriconazole concentrations (1-4, 6-8) and also the effect of therapeutic drug monitoring on treatment outcome (5).

In conclusion, the performance of voriconazole therapeutic drug monitoring can still be improved although voriconazole concentrations were monitored in most patients. A multidisciplinary approach - for instance by means of antifungal stewardship will probably be able to overcome encountered problems like timing of sampling, incompleteness of data on clinical context and lack of implementation of recommendations.

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