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Veringa, Anette

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04
Bioavailability of voriconazole in hospitalised patients

Anette Veringa
Sanne Geling
Lambert F. Span
Karin M. Vermeulen
Jan G. Zijlstra
Tjip S. van der Werf
Jos G.W. Kosterink
Jan-Willem C. Alffenaar

Abstract

An important element in antimicrobial stewardship programmes is early switch from intravenous (i.v.) to oral antimicrobial treatment, especially for highly bioavailable drugs. The antifungal agent voriconazole is available both in intravenous and oral formulations and bioavailability is estimated to be >90% in healthy volunteers, making this drug a suitable candidate for such a transition. Recently, two studies have shown that the bioavailability of voriconazole is substantially lower in patients. However, for both studies various factors that could influence the voriconazole serum concentration, such as inflammation, concomitant intake of food with oral voriconazole, and gastrointestinal complications, were not included in the evaluation. Therefore, in this study a retrospective chart review was performed in adult patients treated with both oral and i.v. voriconazole at the same dose and within a limited (≤5 days) time interval in order to evaluate the effect of switching the route of administration on voriconazole serum concentrations. A total of 13 patients were included. The mean voriconazole trough concentration was 2.28 mg/L [95% confidence interval (CI) 1.29–3.26 mg/L] for i.v. voriconazole administration and 2.04 mg/L (95% CI 0.78–3.30 mg/L) for oral administration. No significant difference was found in the mean oral and intravenous trough concentrations of voriconazole ($P = 0.390$). The mean bioavailability was 83.0% (95% CI 59.0–107.0%). These findings suggest that factors other than bioavailability may cause the observed difference in voriconazole trough concentrations between oral and i.v. administration in the earlier studies and stress the need for an antimicrobial stewardship team to guide voriconazole dosing.

4.1 Introduction

Antimicrobial stewardship (AMS) programmes have been developed to improve antimicrobial use [1]. These programmes mainly focus on antibiotics, whilst antifungal agents receive less attention. However, the treatment of invasive fungal infections remains challenging. Effective treatment may be compromised by toxicity and azole resistance [2].

An important aspect of AMS is the switch from intravenous (i.v.) to oral antimicrobial treatment. For highly bioavailable drugs, early switch from i.v. to oral treatment is suggested because it improves patient comfort and mobility, reduces the incidence of adverse effects related to i.v. administration, reduces the time spent on preparing i.v. medication, and reduces purchasing costs [3]. Even if a hospital has no AMS programme, it is still worthwhile to switch from i.v. to oral treatment based on the abovementioned advantages.

Voriconazole, an antifungal agent generally accepted as the first-line treatment for invasive aspergillosis, is available both in i.v. and oral formulations [4]. The package leaflet recommends a weight-based i.v. maintenance dose of 3–4 mg/kg twice daily or an oral maintenance dose of 200 mg twice daily [5].

Table 1. Factors influencing voriconazole serum concentration [4,7]

Increased voriconazole serum concentration	Reduced voriconazole serum concentration
Increasing age	Non-compliance
Increasing daily dose	Malabsorption
Hepatic impairment	Concomitant intake of food with voriconazole
CYP2C19 poor or intermediate metabolizer	CYP2C19 ultra-rapid metabolizer
DDI: CYP450 inhibitor	DDI: CYP450 inducer
Inflammation	

Abbreviations: DDI: drug-drug interactions

The efficacy of voriconazole and the occurrence of adverse events are associated with the voriconazole serum concentration [6]. However, in clinical practice, highly variable serum concentrations are observed during treatment. Table 1 gives an overview of factors influencing voriconazole serum concentrations [4,7]. Because serum concentrations are highly variable, therapeutic drug monitoring (TDM) is recommended [1,8].

The bioavailability of this antifungal agent is high and is estimated to be >90% in healthy volunteers [4]. Therefore, voriconazole would be an excellent candidate for early switch to oral treatment if clinically justified. However, two studies have recently shown that the bioavailability of voriconazole in patients is substantially lower than previously shown in healthy volunteers [9,10]. This reduced bioavailability could be caused by the changed pharmacokinetics of a drug in patients compared with healthy volunteers [11]. Although both studies in patients showed decreased bioavailability, several factors that could have influenced the pharmacokinetics of voriconazole and hence the voriconazole serum concentration were not included in the evaluation, e.g. inflammation, concomitant intake of food or enteral tube feeding, and

gastrointestinal complications [4,12]. In addition, a large variability of voriconazole serum concentrations is also seen over time, indicating intrapatient pharmacokinetic variability [13]. These factors might haveinfluenced the results of previous studies. Therefore, we performed a retrospective study with strict inclusion criteria to evaluate the effect of switching the route of administration on voriconazole serum concentrations in hospitalised patients.

4.2 Methods
4.2.1 Study design
A retrospective chart review was performed at the University Medical Center Groningen (Groningen, The Netherlands) between January 2009 and December 2014. Patients were included if they were aged ≥18 years, were treated with both i.v. and oral voriconazole, and had a steady-state voriconazole trough concentration for both routes of administration within a 5-day time interval. Steady-state was assumed to be achieved within 24 h if two loading doses of voriconazole were administered or after ten dosages without a loading dose [4]. If the dose or the route of administration was changed, steady-state was assumed to be achieved after at least two dosages, which

is equivalent to ca. 4–5 times the elimination half-life of voriconazole [4]. Furthermore, the difference in dosage between i.v. and oral administration of voriconazole had to be <10%.

Patients were excluded if they suffered from severe diarrhoea or vomiting or if they had ingested food or received enteral tube feeding with voriconazole during oral treatment. Patients were also excluded in the case of concomitant use of a strong CYP3A4 inducer or inhibitor as described in the summary of product characteristics.

This study was evaluated by the local ethics committee (Institutional Review Board 2013-491) and was, according to Dutch law, allowed owing to its retrospective nature.

4.2.2 Data collection

Information regarding voriconazole treatment was collected from patients' medical charts. Furthermore, laboratory parameters were collected that may influence the voriconazole trough concentration, including liver enzymes and C-reactive protein.

Routinely collected voriconazole trough concentrations were measured using a validated and verified liquid chromatography–tandem mass spectrometry (LC-MS/MS) method [14,15]. Bioavailability was calculated as (trough concentration oral × dose i.v.)/(trough concentration i.v. × dose oral).

4.2.3 Statistical analysis

Normally distributed data are presented as the mean and 95% confidence interval (CI), and non-normally distributed data as the median and interquartile ranges (IQR). To determine whether data were normally distributed, a Shapiro–Wilk test was performed. Statistical analyses were performed with a paired sample t-test for normally distributed data and a Wilcoxon signed-rank test for non-normally distributed data. All statistical analyses were performed using SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY). A P-value of <0.05 was considered statistically significant.

4.3 Results

Thirteen patients (eight males) were included in this study. The median patient age was 58 years (IQR 43–64 years). Eleven patients received voriconazole for treatment of a fungal infection and two patients received voriconazole as prophylaxis. Twelve patients received the same dose of voriconazole intravenously and orally. For one patient the difference in voriconazole dose was <10%. The mean dose that patients received was 3.8 mg/kg (95% CI 2.6–4.9 mg/kg) twice daily both for i.v. and oral treatment. Seven patients had a haematological malignancy, five patients had undergone solid organ transplantation and one patient had a pulmonary disease. Additional patient characteristics and results are summarised in Table 2. As shown in this table, no significant difference was found in mean voriconazole trough concentrations (C_{min}) between patients receiving oral and i.v. administration of voriconazole (P = 0.390). The mean bioavailability was 83.0% [95% CI 59.0–107.0%; coefficient of variation (CV) 47.8%].

In total, seven patients used esomeprazole or omeprazole as concomitant medication during voriconazole treatment. To assess esomeprazole or omeprazole as a confounding factor, the population was stratified for concomitant use of these drugs during treatment with voriconazole. No significant difference was found between the two groups.

Table 2. Comparison of patient characteristics within patients treated with both intravenous and oral voriconazole in a limited time interval (n= 13).

	Intravenous	Oral	P-value[a]
ALP	106 (86 – 174)[b]	109 (93 – 171)[1]	0.916[c]
ALT	38 (23 – 88)[b]	42 (23 – 99)[1]	0.139[c]
AST	44 (29 – 59)	40 (26 – 53)	0.117
γ-GT	134 (84 – 306)[b]	119 (85 – 302)[1]	0.382[c]
Total bilirubin (μmol/L)	13 (8 – 24)[b]	13 (10 – 25)[1]	0.964[c]
CRP	38 (22 – 54)	40 (22 – 58)	0.782
Albumin (g/L)	30 (25 – 34)	29 (25 – 33)	0.894
C_{min}	2.28 (1.29 – 3.26)	2.04 (0.78 – 3.30)	0.390

Abbreviations: ALP: alkaline phosphatase (U/L), ALT: alanine transaminase (U/L), AST: aspartate transaminase (U/L), γ-GT: gamma-glutamyltransferase (U/L) CRP: C-reactive Protein (mg/L), C_{min}: voriconazole trough concentration (mg/L). Data are presented as mean (95% confidence interval) unless specified otherwise. [a] Statistical analysis are performed with a paired sample t-test unless specified otherwise. [b] Median (interquartile range). [c] Wilcoxon signed-rank test.

4.4 Discussion

No significant difference was found in mean voriconazole trough concentrations in individual patients who were treated with both i.v. and oral administration of voriconazole within a limited time interval (P = 0.390). Furthermore, the bioavailability of voriconazole in this study (83.0%; CV 47.8%) appeared slightly reduced compared with the bioavailability in healthy volunteers (96%; CV 13%) [5].

The bioavailability observed in patients in the current study was higher than the bioavailability previously found by others [9,10]. Altered bioavailability can be explained by several factors. For instance, mucositis is a common complication seen in patients with haematological malignancies, caused by chemotherapy. Diarrhoea, which is associated with gastrointestinal mucositis, can lower bioavailability and hence the serum concentration of drugs following oral administration. Therefore, the moment when i.v. treatment of a drug is changed to oral treatment should be considered carefully. Another complication that is commonly seen in solid organ transplant recipients and in patients with haematological malignancies is infection. The degree of inflammation appears to be associated with higher voriconazole trough concentrations [12]. Therefore, voriconazole trough concentrations are probably higher in the initial phase of an infection and are likely to decrease during recovery. Because it is recommended to start with i.v. treatment and switch to oral treatment if this is clinically justified [5], higher voriconazole trough concentrations appear partly explained by the inflammation coinciding with i.v. treatment. Furthermore, food intake concomitant with oral administration of voriconazole reduces the bioavailability of voriconazole by ca. 20%. Therefore, it is recommended to take oral voriconazole at least 1 h before or after meals [4]. In this retrospective study, patients were excluded if any of the factors mentioned above were applicable.

To minimise other factors that could influence the voriconazole serum concentration, such as CYP2C19 genotype or underlying disease, patients were only included if a voriconazole trough concentrationwas measured for both routes of administration. However, it should be mentioned that the bioavailability of voriconazole appears higher in poor metabolisers of CYP2C19 compared with extensive metabolisers [16]. Although we did not determine the CYP2C19 genotype in this study, it is unlikely that this affected the results since all included patients were Caucasian and only ca. 3–5% of the Caucasian population are poor metabolisers [17]. Therefore, it is unlikely that the higher bioavailability observed was caused by poor metabolism of voriconazole.

It was recently shown that the bioavailability of voriconazole can also be influenced by the voriconazole dose [18]. Here, bioavailability of voriconazole for patients receiving 50 mg voriconazole was substantially lower compared with bioavailability for patients receiving 400 mg. However, a voriconazole dose of 50 mg is not a standard voriconazole dose given in clinical practice. With an average body-weight of 70 kg, a dose of 50 mg corresponds to a dose of 0.70 mg/kg. In the current study, a mean voriconazole dose of 3.8 mg/kg was given. Therefore, we expect minimal influence of the voriconazole dose on bioavailability.

In our hospital, TDM of voriconazole is routinely performed. Therefore, selection bias seems negligible. However, this retrospective study has some important limitations. First, voriconazole trough concentrations were used to estimate the bioavailability and to determine whether there was a difference in voriconazole exposure between i.v. and oral administration of voriconazole. Usually, bioavailability is determined using the area under the concentration–time curve (AUC), as trough concentrations will be less accurate. However, the voriconazole trough concentration gives a good estimation of the AUC [10,19]. Another important limitation is the small sample size of this retrospective study. This was predominantly caused by the strict inclusion criteria. Since voriconazole shows nonlinear pharmacokinetics and has a large variability in serum concentration over time, these strict inclusion criteria were chosen. Furthermore, esomeprazole or omeprazole was the only potential interacting co-medication used by patients in this study [4]. The impact of this inhibitor of CYP2C19 on the voriconazole trough concentration and consequently on the AUC is probably negligible because no significant difference was found between patients who used esomeprazole or omeprazole and those who did not use these drugs during treatment with voriconazole.

4.5 Conclusion
Although this study has some important limitations, the data give an indication that the switch from i.v. to oral voriconazole can be made without decreasing serum concentrations. Bioavailability appears slightly lower in hospitalised patients compared with healthy volunteers, but remained high when factors that could have influenced the bioavailability were eliminated. For antibiotics, early switching programmes are part of AMS. Patients who are part of these programmes should be ensured of the continued efficacy of their treatment. Since oral treatment has some advantages over i.v. treatment as discussed previously, we suggest that early switching programmes should be applied in treatment with voriconazole, taking into account all factors influencing voriconazole concentrations and its complex pharmacokinetics.

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