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Short Communication

Bioavailability of voriconazole in hospitalised patients

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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 i.v. 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 i.v. 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.

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]. 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

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Table 1
Factors influencing voriconazole serum concentrations [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 metaboliser	CYP2C19 ultra-rapid metaboliser
DDI: CYP450 inhibitor	DDI: CYP450 inducer
Inflammation	

DDI, drug–drug interaction.

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 have influenced 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.

2. Methods

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.

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).

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.

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 among patients treated with both intravenous (i.v.) and oral voriconazole in a limited time interval ($n = 13$).

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

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; CRP, C-reactive protein; C_{min}, voriconazole trough concentration.
Data are presented as the mean (95% confidence interval) unless specified otherwise.
[a] Statistical analysis was performed with a paired sample *t*-test unless otherwise specified.
[b] Median (interquartile range).
[c] Wilcoxon signed-rank test.