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Neurological adverse events to voriconazole: evidence for therapeutic drug monitoring

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Summary

Background: Voriconazole shows a considerable interpatient variation of serum concentrations.

Methods and result: In an analysis of 28 treatment courses, 6 patients presented with neurological adverse events (hallucination, encephalopathy, and visual disturbance). The hazard ratio per 0.1 µg/mL voriconazole serum level (sVL) increase was 2.27 (95% CI: 1.45–3.56, p <0.001). There was no correlation between sVL and creatinine (r = 0.12, p = 0.114), ALT (r = –0.14, p = 0.072), AST (r = 0.003, p = 0.964), alkaline phosphatase (r = 0.03, p = 0.723).

Conclusions: Our findings demonstrate that elevated sVL is associated with neurological adverse events, and measurement of its serum concentration could improve voriconazole treatment and safety.

Key words: voriconazole; side effects; drug monitoring

Introduction

Invasive fungal infection is a devastating disease in leukaemia and stem cell transplant patients with a high morbidity and mortality [1]. Treatment with voriconazole (VOR), a broad-spectrum second-generation azole antifungal agent, has been shown to result in favourable outcomes in the setting of multiple opportunistic fungal infections, including those caused by *Aspergillus* species and less-common invasive fungi, such as *Fusarium* species [2, 3]. Voriconazole is generally well tolerated. The most common side effect, which was not previously seen with other azoles, is a reversible disturbance of vision (photopsia), including altered colour discrimination, blurred vision and photophobia. These transient side effects occur in 20–30% of patients, and hardly result in discontinuation of therapy [4–6].

Elevations in liver enzymes occur also with VOR therapy. Most patients have asymptomatic elevation of hepatic enzyme levels, but several patients with severe life-threatening hepatitis have been described. A statistically significant risk of elevated aspartate transaminase, alkaline phosphatase, but not alanine transaminase abnormalities for severe liver toxicity was recently shown. The risk of developing elevated liver enzymes appeared to increase with increased serum VOR levels (sVL) and resolved with discontinuation of treatment with the drug [4, 7, 8].

Voriconazole is metabolised via the CYP450 enzyme family. The activity of the CYP2C19 pathway, which is the major metabolic pathway for VOR, is highly dependent on genetic polymorphism. 15–20% of patients of Asian descent and 3% of patients of European descent have low CYP2C19 activity [9] resulting in VOR levels as much as 4 times higher than those noted in subjects who metabolise the drug more extensively. In the elderly population (>65 years) sVL tended to be higher than in subjects aged 45 years or less [10]. However, presently there are no recommendations of dosage adjustments or routine monitoring of sVL. Recent observations suggest that hepatic toxicity and visual disturbance might be dose related [4, 7, 11]. In this study, we present a retrospective analysis of our experiences with VOR therapeutic drug monitoring, which revealed a dose dependent occurrence of neurological adverse events.

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Patients and methods

We retrospectively analyzed the clinical records of 26 patients at the University Hospital of Zürich who were treated with VOR and had 2 consecutive measured VOR serum levels between 1/1/2004 and 2/20/2006. During this period, patients received VOR for primary therapy of proven IA, probable IA (as defined by consensus criteria [12]) or invasive candidiasis. Age, gender, underlying disease, type of stem cell transplantation (SCT), severity of graft versus host disease (GVHD) [13], and use of cyclosporine, tacrolimus, and antibiotics were recorded. A neurologist evaluated each patient with suspected neurological adverse event (nAE).

Steady-state serum VOR trough levels were monitored using a HPLC assay [14], 3 days to 14 months (median 40 days) after starting or changing the VOR doses. The lower limit of quantification was set at 0.1 µg/mL; concentrations below that limit were recorded as 0 in the analyses.

Continuous variables were expressed as median (range). Man-Whitney U test was used to compare continuous variables. Correlations between measured sVL and transaminase levels were investigated with Spearman rank correlation testing. An univariable Cox proportional hazards regression model was used to evaluate risk factors for the probability of neurological adverse events (nAE) and to adjust for the duration of VOR treatment as well as to incorporate time-dependent variables into the model. The first day of VOR treatment was the start of follow-up time. Patients were censored at the time of occurrence of nAE. Only the first episode during follow-up was included. Potential covariates included age, sex, disease, development of GVHD, exposure to cyclosporine or tacrolimus, and transaminase levels. P values <0.05 were considered statistically significant. We used logistic regression to analyze the association between the cyclosporine/tacrolimus treatment and sVL. All statistical analyses were conducted using Stata 8.2 (Stata Corporation, College Station, Texas; USA).

Results

Study population: Twenty-six patients were treated with VOR during the observation period. Nineteen (73%) were male, the median age was 47.5 (range 22–61) years. The most frequent underlying disease was acute myeloid leukemia (23 patients, 88,5%). One patient was included with myelodysplastic syndrome, one with aplastic anaemia, and one with multiple myeloma. Four-

Table 1

Characteristics of patients (six patients of the present study and 3 patients of previously published reports) with neurological adverse events during treatment with voriconazole

Age	Sex	Underlying condition	Clinical presentation	Immuno-suppression	Voriconazole dosage	Serum vori-conazole level	Duration of VOR-treatment (days)	Outcome improvement*/ duration of symptoms after VOR stop	Reference
43	f	liver transplantation	painful peripheral neuropathy	cyclo, mmf, pred	N/A	N/A	70	++/ 2 weeks	[17]
78	m	AML	musical hallucinations	None	300 mg bid	N/A	6	+++/ 3 days	[18]
76	m	pulmonary fibrosis	confusion visual hallucinations	pred	4 mg/kg bid iv	8.96	3	+++/ 24 hours*	[19]
40	m	AML	hypotonia anxiety, insomnia	None	200 mg bid	1.5	7	+++/ 3 days	present report
57	w	AML	visual hallucinations asthenia nystagmus	None	300 mg bid	6.4	4	+++/ 3 days	present report
61	m	AML	irritability, impaired concentration, asthenia	None	200 mg bid	5.7	4	improved spontaneously during treatment	present report
50	m	AML, SCT (m/r)	visual hallucinations asthenia	cyclo, pred	300 mg bid	5.7	22	+++/ 4 days	present report
58	m	AML, SCT (m/r)	visual disturbance	cyclo, mmf, pred	300 mg bid	2.3	3 (75)**	improved spontaneously during treatment	present report
49	m	aplastic anaemia, SCT (m/r)	dysarthria asthenia, insomnia	cyclo, pred	200 mg bid	6.5	13	+++/ 4 days***	present report

iv = intravenously, VOR = voriconazole, cyclo = cyclosporine, mmf = mycophenolate mofetil, pred = prednisone, SCT = stem cell transplantation, m/r = matched/related. N/A = not available, ++ improvement with residuals, +++ complete improvement, * 24 hours after 20% dose reduction, ** 3 days after dosage adjustment, 75 days after start of VOR treatment, ***symptoms reappeared 3 days after VOR restart

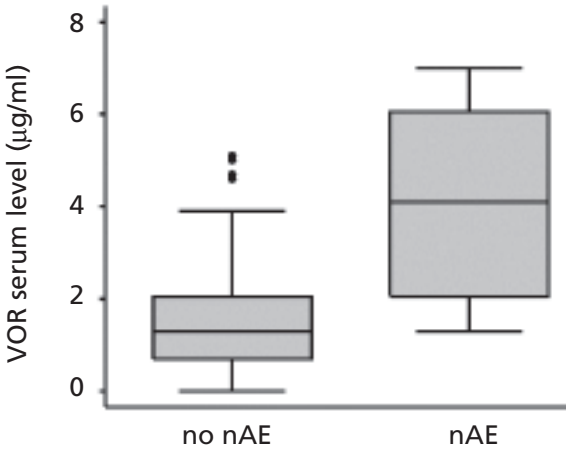

Figure 1

Box-plot of trough voriconazole levels in patiens with and without neurological adverse events (nAE). Thick bar, median level; box, interquartile range (IQR); whiskers, minimum and maximum levels after exclusion of outliers; dots, outliers (values that are more than the third quartile plus 1.5 × IQR).

teen patients were treated for possible invasive aspergillosis (IA), 5 for probable IA, 4 for proven IA, 2 for hepato-splenic candidiasis and one patient for a catheter related candidaemia due to *C. krusei*. All patients had at least one course of antibiotic treatment. Ten patients were treated with cyclosporine in combination with prednisone and 2 with tacrolimus and prednisone. All of these patients underwent HLA matched related SCT, and 5 of them were treated for acute or chronic GVHD.

Voriconazole Levels: A total of 176 sVL were measured in 26 patients during 28 treatment courses. Median number of obtained sVL per patient was 6 (2–22) samples. sVL-levels ranged from 0 to 7 µg/mL (median: 1.4 µg/mL). In patients receiving 200 mg bid levels ranged from 0 to 7 µg/mL (median: 1.55 µg/mL), and from 0.1 to 6.8 µg/mL (median: 1.5 µg/mL) in patients receiving 300 mg bid or 400 mg bid, respectively.

In 14 patients at least one sVL was measured >3.0 µg/mL (median 3.75 µg/mL, range 3 µg/mL –7 µg/mL), and in 7 patients at least one sVL >4 µg/mL (median 5.6 µg/mL, range 4.6 µg/mL –7 µg/mL), respectively. nAE occurred in 4 patients with nAE >4 µg/mL (table 1).

There was no correlation between sVL and creatinine (r = 0.12, p = 0.114), ALT (r = –0.14, p = 0.072), AST (r = 0.003, p = 0.964) and alkaline phosphatase (r = 0.03, p = 0.723). No significant association for elevated sVL was found neither with cyclosporine treatment (OR per 0.1 µg/mL increase of sVL: 1.24, 95% confidence-interval (CI): 0.93–1.66, p = 0.140) nor tacrolimus treatment (OR: 0.92, 95% CI: 0.78–1.08, p = 0.303).

Neurological adverse events: Neurological adverse events were observed in 6 patients. The symptoms and course were summarised in table 1. The occurrence of neurological symptoms was significantly associated with elevated sVL (hazard ratio per 0.1 µg/mL increase of sVL: 2.27, 95% CI: 1.45–3.56, p <0.001). sVL were significantly increased (p <0.001) in patients with nAE (figure 1). All nAE occurred within 3 to 22 days (median: 7 days) after start of VOR treatment or dosage adjustment. No association was found with sex, GVHD, antibiotic-, cyclosporine- or tacrolimus-treatment.

Discussion

Voriconazole, a broad-spectrum triazole antifungal agent, is an appropriate choice for therapy of invasive aspergillosis and candidiasis. The VOR treatment is generally well tolerated. However, clinicians should be aware of the potential neurological adverse events during VOR treatment. Voriconazole exhibits nonlinear pharmacokinetics, possibly related to saturation of metabolism, and substantial intersubject variability in serum concentrations is found [5].

We have recognised 6 patients receiving VOR therapy who developed encephalopathy, with unspecific symptoms such as fatigue, impaired concentration, loss of memory, insomnia, anxiety, irritability, dysarthria, visual disturbance, and hallucinations.

Our results demonstrated a statistically significant association for every 0.1 µg/mL increase in sVL and the occurrence of nAE. In a ROC curve (data not shown) for sVL and nAE, there are positive and significant deviations from the line of identity, indicating that VOR concentrations can be used to identify a high proportion of cases at risk for the development of nAE, with a few false positives. Recently, a study showed that nAE occurred in 50% of patients with sVL >5.5 µg/mL, but no direct association with sVL increase was shown [11]. As table 1 demonstrates, in our study two patients were diagnosed with nAE with sVL <5.5 µg/mL. However, nAE occurred in all patients with sVL >5.5 µg/mL.

In our study 75% of measured sVL were above 1 µg/ml, which is well beyond the MICs for *Candida* spp. (0.001–0.39 µg/ml) and VOR MIC breakpoints for *Candida* spp. (<1.0 µg/mL = susceptible), or *Aspergillus* spp. (0.35–0.58 µg/ml) [15, 16]. Therapeutic drug monitoring of sVL with target drug levels between 1 µg/ml and 4 µg/ml could therefore be applied to increase efficiency and safety of VOR treatment.

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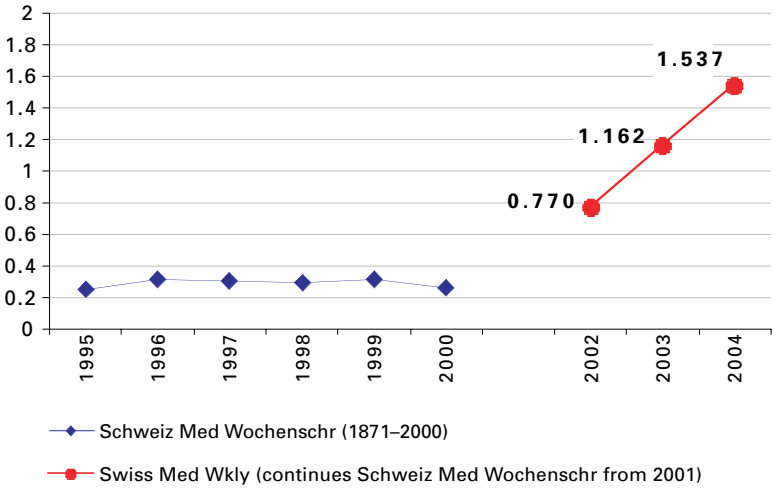

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