Neurological adverse events to voriconazole: evidence for therapeutic drug monitoring

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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.
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

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

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 patients 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).

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.
References

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