Voriconazole Pharmacokinetics and Therapeutic Drug Monitoring: A Multi-Center Study

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Keywords: Voriconazole, Therapeutic Drug Monitoring, Pharmacokinetics,
Glucocorticoids, Fungal infection, Pharmacodynamics
Abstract

Voriconazole is a first line agent in the treatment of many invasive fungal infections and is known to display highly variable pharmacokinetics. Previous studies of voriconazole therapeutic drug monitoring (TDM) have suggested concentration monitoring to be clinically useful but have been limited by small patient samples at a single institution. This multi-center retrospective study aimed to investigate relationships between voriconazole concentration and clinical outcomes and adverse events, and assess clinical factors and drug interactions that may affect voriconazole concentration. Medical records were reviewed for patients who received voriconazole and had ≥1 concentration measured at seven hospitals in Australia. The study included 201 patients with 783 voriconazole trough concentrations. Voriconazole concentrations <1.7 mg/L were associated with a significantly greater incidence of treatment failure (19/74 patients [26%]) than at concentrations ≥1.7 mg/L (6/89 patients [7%] p<0.01). Neurotoxic adverse events (visual and auditory hallucinations) occurred more frequently at voriconazole concentrations >5 mg/L (10/31 patients [32%]) than at concentrations ≤5 mg/L (2/170 patients [1.2%] p<0.01). Multiple regression analysis of voriconazole concentration identified associations between increasing patient weight, oral administration of voriconazole and co-administration of phenytoin or rifampicin with significantly reduced concentrations, with increasing patient age and co-administration of proton pump inhibitors associated with increased concentrations. Co-administration of glucocorticoids was found to significantly reduce voriconazole concentrations, inferring a previously unreported drug interaction between glucocorticoids and voriconazole.
The triazole antifungal voriconazole is widely used in the treatment of invasive fungal infections (IFIs) due to its broad coverage of pathogenic yeasts and molds, and evidence of superiority over amphotericin B in the primary treatment of invasive aspergillosis (12). Voriconazole is known to exhibit highly variable non-linear pharmacokinetics, and is metabolized primarily via CYP2C19 and to a lesser extent CYP3A4 and CYP2C9 (27). In agreement with other azole antifungals, in vitro studies have found the unbound drug area under the concentration-time curve divided by the MIC \((fAUC/MIC)\) ratio is the pharmacokinetic/pharmacodynamic measure that is most predictive of voriconazole efficacy in murine models of candidiasis (1), and may be a useful metric in aspergillosis (17).

Therapeutic drug monitoring (TDM) is used to guide therapy for a number of clinically important medicines, both in improving response to therapy by individualizing dose regimens or by preventing drug-related adverse events. A number of studies have demonstrated a relationship between voriconazole plasma concentrations and clinical efficacy and toxicity (2, 21, 31), with a therapeutic concentration range between 1.0 and 5.5 mg/L advocated to improve treatment outcome and minimize the risk of neurotoxic adverse events (22).

Despite this, previous studies of voriconazole TDM have generally been limited by small sample size, and typically have only investigated patients from a single institution (14, 19, 22, 25, 28, 29, 32). Furthermore, while CYP2C19 genotype has been identified as an important determinant of voriconazole pharmacokinetics in healthy volunteers (33), few studies have assessed the potential impact of clinical factors and drug interactions
on voriconazole concentration in patients receiving treatment with voriconazole. This study aimed to investigate relationships between voriconazole concentrations, clinical outcomes and adverse events using a multi-center retrospective design. Furthermore, clinical factors and drug interactions that may affect voriconazole concentration were also investigated.

Materials and Methods

Patient enrollment and data collection. Patients aged 18 years or older who received voriconazole and had at least one voriconazole concentration measured during therapy at seven hospitals in Australia between December 2008 and May 2010 were eligible for inclusion. All voriconazole concentration data was collected from a central referral laboratory (SydPath, St Vincent’s Hospital, Sydney). A validated high-performance liquid chromatography (HPLC) assay was used to measure voriconazole concentrations (6). Patient medical records were individually reviewed using a standardized data collection template at each study site to collect demographic information and clinical data on outcomes of therapy and adverse events, as well as voriconazole dosing information and concomitant medications taken during voriconazole therapy. The study received multi-site ethics approval from the Sydney Local Heath District - Concord Repatriation General Hospital Human Research Ethics Committee.

IFI classification and treatment outcome. The 2008 guidelines from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group were used to classify IFI as proven,
probable or possible (8). Treatment success was assessed based on partial or complete improvement in clinical (symptoms of infection, fever) and radiological signs (Computed Tomography, High Resolution Computed Tomography or Magnetic Resonance Imaging) findings) of infection. Treatment failure was defined as persistent or progressing IFI based on clinical and radiological signs or continuing positive cultures, or death due to IFI after at least 7 days therapy with voriconazole.

**Statistical analysis.** Voriconazole dosing records for each patient were used to verify the time of voriconazole concentration sampling in relation to dose. As trough concentrations are recommended for voriconazole TDM (2) and to avoid the confounding effect of differing sampling times post-dose, non-trough voriconazole concentrations (sampled >2 hours before the next dose) were excluded from the analysis. In patients who received an intravenous or oral voriconazole loading dose, trough concentration measurements taken on Day 2 of dosing or later were included in the analysis. In patients who did not receive a loading dose, trough concentration measurements taken on Day 7 of dosing or later were included in the analysis. The median voriconazole concentration was used to assess relationships between concentration and treatment outcome. The relationship between voriconazole concentration and treatment outcome was assessed in both the overall treatment population, including patients receiving voriconazole for the treatment of a proven, probable or possible IFI, localized fungal infection or for empiric antifungal therapy, and in a subset of patients receiving voriconazole for the treatment of a proven or probable IFI.
Receiver operating characteristic (ROC) curves were used to explore the relationship between voriconazole concentration and treatment outcome or reported adverse events. A multiple linear regression analysis was used to identify factors that contribute to the variability in voriconazole concentration. Elevations in liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase and bilirubin) were assessed and graded using the Common Terminology Criteria for Adverse Events (CTCAE) V4.03 (20). Univariate analyses were performed using the Mann-Whitney U test or Wilcoxon Signed Rank test as appropriate due to the non-normality of voriconazole concentration. Proportions were compared using the chi-squared or Fisher’s exact test as appropriate. Statistical significance was defined by a P value of <0.05. Statistical analyses were performed with PASW Statistics 18 (SPSS Inc., Chicago, IL).

Results

Patient characteristics. A total of 201 patients were included in the study. The majority of patients received voriconazole for the treatment of a known or presumed fungal infection (170/201 [85%]) compared to prophylaxis against fungal infections (31/201 [15%]). Hematological malignancy was the most common underlying condition in patients receiving voriconazole (118/201 [59%]); among these patients acute myeloid leukemia was the most common condition (n=47). Demographic information, indication for therapy, underlying conditions and site of infection are included in Table 1. Among patients receiving voriconazole for a proven or probable IFI (n=67), Aspergillus was the most common fungal pathogen (38/67 [57%]) with *A. fumigatus* the
most commonly identified species. Thirteen patients received voriconazole for treatment of *Scedosporium* (nine *Scedosporium apiospermum*, two *Scedosporium prolificans*, two species not identified); 10 patients were treated for infections due to *Candida* (three *C. glabrata*, two *C. tropicalis*, two *C. glabrata* and *C. tropicalis*, one *C. albicans*, two species not identified). The yeast *Cryptococcus* was identified for five patients (two *C. gattii*, one *C. neoformans*, two species not identified), with less common fungal pathogens identified for two patients (*Bipolaris* spp. and *Fusarium* spp./*Paecilomyces lilacinus*). Two patients were treated with voriconazole for unidentified invasive mold infections.

**Voriconazole therapy.** A total of 783 voriconazole trough concentrations from 201 patients were included in the analysis. Median voriconazole concentration was 1.4 mg/L (range; 0–14.3 mg/L). Voriconazole was administered orally to 48% of patients (97/201), with 76 patients receiving both intravenous and oral voriconazole during treatment; 28 patients received only intravenous voriconazole. The median maintenance dose of voriconazole was 6.1 mg/kg/day (range; 2.4–17.4 mg/kg/day). The median number of trough concentrations measured per patient was 2 (range; 1–22). The relationship between voriconazole daily dose and trough concentration was highly variable (Figure 1).

**Voriconazole concentration and treatment outcome.** Among patients receiving voriconazole for the treatment of a suspected or confirmed fungal infection (n=170) treatment outcome was evaluable for 163 patients. Twenty-five patients failed therapy (15.3%); median voriconazole concentration was significantly lower in patients failing therapy (0.9 mg/L) compared to those treated successfully (2.1 mg/L, p<0.05). A higher rate of treatment failure was observed in patients with proven or probable IFI (14/67, 20.9%); voriconazole concentration was lower in cases of treatment failure compared to
treatment success (0.9 vs. 2.0 mg/L, p<0.05). ROC curve analysis indicated that voriconazole concentration was a significant predictor of treatment success in both the treatment population and the proven or probable IFI subset; a voriconazole concentration of ≥1.7 mg/L minimized the incidence of treatment failure (Figures 2A and 2B). The incidence of treatment failure is described in Table 2. No patient receiving voriconazole as antifungal prophylaxis developed a breakthrough IFI in this study.

Voriconazole concentration and adverse events. Neurotoxic adverse events characterized by visual or auditory hallucinations were reported in 21 patients (10.5%) during voriconazole therapy. The median number of days from time of voriconazole initiation to onset of hallucinations was 4 days (range; 1–52 days). Of the 21 patients experiencing neurotoxic adverse events, 11/21 (52%) were receiving intravenous voriconazole at the time of onset, with 10/21 (48%) administered oral voriconazole. Trough voriconazole concentrations were measured at the time of this adverse event in 12 patients and were significantly higher than median voriconazole concentrations in patients not experiencing hallucinations (median; 6.5 vs. 1.6 mg/L, p<0.01). ROC curve analysis indicated that voriconazole concentration was a significant predictor of neurotoxic adverse events and a voriconazole concentration of ≤5 mg/L was found to minimize the incidence of neurotoxic adverse events (Figure 2C). The incidence of visual or auditory hallucinations is described in Table 2. All occurrences of neurotoxicity resolved following voriconazole cessation or dose reduction.

Data on liver function tests measured on one or more occasions during voriconazole therapy was available for 86% of patients (173/201); data on baseline LFTs prior to voriconazole dosing was available for 46% of patients (93/201). At baseline, 68% of
patients (63/93) had elevated LFTs meeting the criteria of CTCAE grade 1 or higher.

During voriconazole therapy, 87% of patients (151/173) had CTCAE grade 1 LFT elevation, with 60% meeting grade 2 criteria, 41% grade 3 and 11% grade 4. Voriconazole concentration was not significantly different in patients with elevated LFTs (using CTCAE grade 1, 2, 3 or 4 cutoff values (20)) compared to patients without LFT elevation.

**Factors affecting voriconazole concentration.** A multiple linear regression analysis identified a number of clinical factors and drug interactions associated with a significant change in voriconazole concentration (Table 3). Increasing patient age, increasing daily dose and concomitant administration with any proton pump inhibitor (omeprazole, pantoprazole, esomeprazole or rabeprazole) were associated with significantly increased voriconazole concentrations; factors associated with reduced voriconazole concentration included oral administration of voriconazole (compared to intravenous), increasing patient weight, co-administration with rifampicin or phenytoin, and co-administration with a glucocorticoid (prednisone/prednisolone, methylprednisolone or dexamethasone). Evidence for an interaction between voriconazole and glucocorticoids has not previously been reported, thus a univariate analysis of the effect of glucocorticoids on voriconazole concentration was performed (Table 4). The analysis of data from this study suggests that all glucocorticoids significantly reduce voriconazole concentration, with co-administration of methylprednisolone and dexamethasone reducing voriconazole concentration to a greater extent than prednisone or prednisolone.
Discussion

This study is the largest multi-center investigation of voriconazole TDM to date and presents significant evidence of the relationships between voriconazole concentration and clinical efficacy and toxicity, also identifying a number of important clinical factors and drug interactions that predict voriconazole exposure in patients.

In this study voriconazole concentrations below 1.7 mg/L were associated with significantly higher rates of treatment failure (Figure 2A and 2B). This difference was observed both in the overall treatment population (including patients treated empirically and for localized fungal infections) as well as in patients with proven or probable IFIs, where higher rates of treatment failure were observed (Table 2).

Neurotoxic adverse events were relatively common in patients treated with voriconazole (approximately 10%) and usually occurred within several days of commencing voriconazole. Voriconazole concentrations measured at the time of this adverse event in 12 patients were significantly higher than in patients without hallucinations; the majority of neurotoxic adverse events occurred at concentrations above 5 mg/L (Figure 2C and Table 2).

A number of smaller studies of voriconazole TDM have recommended lower and upper concentration limits for voriconazole, with the goal of maximizing treatment success and minimizing drug-related toxicity (Table 5). Pascual and colleagues prospectively studied 52 patients receiving voriconazole for the treatment of known or suspected IFI (22). In this cohort the treatment success rate was significantly higher at voriconazole concentrations >1 mg/L (88%) compared to patients with concentrations ≤1 mg/L (54%). All patients experiencing neurotoxicity in this study had voriconazole
concentrations above 5.5 mg/L (22). A study in children receiving voriconazole for the
treatment of IFI identified a similar efficacy target of >1 mg/L (21).

Ueda et al retrospectively investigated voriconazole TDM in a cohort of 34 patients
with hematological diseases (32). This study identified greater treatment success at
voriconazole concentrations above 2 mg/L in patients without refractory hematological
diseases, also identifying a greater incidence of LFT elevation at voriconazole
concentrations above 6 mg/L (32).

Other studies of voriconazole concentration-effect relationships in patients receiving
treatment for IFIs have identified concentrations of >2.05 mg/L (random sampling) (25)
and >2.2 mg/L (trough sampling) (19) as potential lower concentration limits for
voriconazole therapy. Simulations from a pooled analysis of random voriconazole
concentrations from 9 clinical trials identified a trough/MIC ratio of 2 to 5 was associated
with the highest probability of response (31). The lack of MIC data in this patient cohort
precluded the investigation of trough/MIC ratios, although the clinical utility of this
metric may be limited by its reliance on a fungal MIC measurement being available.

While treatment failures were not identified between 1.7 and 2 mg/L in the present
study, in the context of previous studies (Table 5) aiming for voriconazole trough
concentrations of at least 2 mg/L appears to be a rational recommendation.

Reports of neurotoxicity with voriconazole have generally occurred at high
voriconazole concentrations. Imhof et al reported high voriconazole concentration (>5
mg/L) with four of six cases of neurotoxic adverse events with voriconazole (14); a
further case report of confusion and hallucination on voriconazole reported a
concentration of 8.96 mg/L (4). In addition to neurotoxicity, other common adverse
events with voriconazole include temporary visual disturbances and elevations in hepatic enzyme concentrations (15). Both of these adverse events have been reported more frequently at higher voriconazole concentrations (26), although a significant relationship between voriconazole concentration and LFT elevation was not observed in this study, which may reflect the high incidence of elevated LFTs prior to commencing voriconazole in this study or limitations in the available LFT data. Based on the low frequency of neurotoxic adverse events reported at concentrations ≤ 5 mg/L in the present study and by other authors (14, 22), voriconazole trough concentrations should be maintained below 5 mg/L.

As has been reported by other authors (22) the relationship between voriconazole dose and concentration was highly variable in this study (Figure 1). A multiple linear regression analysis of voriconazole concentrations identified a number of drug interactions, as well as demographic and clinical factors that predict changes in voriconazole concentration (Table 3).

Most notably, the use of a systemic glucocorticoid, including prednisone or prednisolone, methylprednisolone or dexamethasone was associated with significantly reduced voriconazole concentrations, suggesting a previously unreported drug interaction. An in vitro study has identified glucocorticoid receptor binding sites in the promoter region of the CYP2C19 gene and demonstrated up-regulation of CYP2C19 in response to dexamethasone, supporting an inductive effect of glucocorticoids on CYP2C19 (5). An in vivo study has also demonstrated an inductive effect of a 12–15 day course of prednisone on the metabolism of cyclophosphamide, a substrate of both CYP2C19 and CYP2C9 (10). In addition, CYP3A4 contributes to the metabolism of
Voriconazole (27), which glucocorticoids have been shown to induce at higher doses (7).

Taken together, a glucocorticoid-mediated induction of CYP2C19 (and possibly CYP3A4) resulting in increased voriconazole metabolism appears to be a plausible mechanism for this interaction.

While the magnitude of this interaction appears to be less than observed with other known inducers of CYP2C19 such as rifampicin and phenytoin (Table 3), the clinical implications for voriconazole therapy may be significant. In the present study, 47% of patients had at least one voriconazole concentration measured while taking a glucocorticoid, suggesting the use of glucocorticoids in patients taking voriconazole is common. Differences in the degree of interaction observed between different glucocorticoids are also apparent. In both the multiple regression and univariate analysis (Tables 3 and 4), co-administration of dexamethasone and methylprednisolone reduced voriconazole concentrations to a greater extent than prednisone or prednisolone; these results correlate with the higher glucocorticoid receptor potency observed with dexamethasone and methylprednisolone (9).

Voriconazole is reported to have nearly complete oral bioavailability of 96% in healthy volunteers (23), although lower bioavailability has recently been reported in patients (13). Oral administration of voriconazole was associated with significantly lower voriconazole concentrations compared to intravenous voriconazole in this study (Table 3). A study of voriconazole absolute oral bioavailability in healthy volunteers determined a mean value of 82.6%; bioavailability appeared to differ based on CYP2C19 genotype (mean 75.2% [62.9–87.4] in CYP2C19 extensive metabolizers compared to 94.4% [78.8–109.9] in poor metabolizers) (24). Although these differences did not reach statistical
significance, the observed trend towards lower bioavailability in CYP2C19 extensive
metabolizers suggests that CYP2C19 expression in the gut wall may lower voriconazole
exposure (24). While studies of absolute oral bioavailability in patients are lacking, our
data supports the presence of a small but considerable first pass effect for voriconazole,
which may vary based on CYP2C19 genotype.

A significant increase in voriconazole concentrations was observed with all proton
pump inhibitors when co-administered with voriconazole (Table 3). Previous studies have
demonstrated increased voriconazole exposure with omeprazole (34) due to an
inhibition of CYP2C19, however there have been few reports regarding the interaction of
voriconazole with other proton pump inhibitors such as pantoprazole, rabeprazole and
esomeprazole. While pantoprazole and rabeprazole are generally expected to have a
lower drug interaction potential compared to omeprazole (3), all proton pump inhibitors
are known to competitively inhibit CYP2C19 activity in vitro (16). A previous report by
Heinz et al demonstrated higher voriconazole concentrations when co-administered with
pantoprazole (11). The lower regression coefficient determined for pantoprazole (Table
3) suggests a reduced (but still significant) interaction with voriconazole when compared
with other proton pump inhibitors, in agreement with in vitro findings that pantoprazole
is the weakest inhibitor of CYP2C19 (16). Increasing patient age was also found to be a
significant predictor of increased voriconazole concentrations; this finding is consistent
with a previous pooled analysis that found approximately 80–90% higher voriconazole
concentrations in patients aged >65 years compared to younger patients (23).

The results of this study infer a number of novel clinical implications for voriconazole
therapy. In addition to the known CYP2C19 inducers rifampicin and phenytoin, clinicians
should be aware of the potential for reduced voriconazole exposure and subsequent
treatment failure in patients administered systemic glucocorticoids. While previous
reports had identified a significant interaction between omeprazole and voriconazole, we
have found all proton pump inhibitors may lead to increased voriconazole concentrations
and consequent greater risk of neurotoxic adverse events. In the context of previous
studies, these results support a narrow therapeutic range for voriconazole trough
concentrations of between 2–5 mg/L. In light of the highly variable pharmacokinetics
observed with voriconazole, established concentration-efficacy and toxicity relationships
and significant drug interactions, therapeutic drug monitoring is fundamental to the
optimal use of voriconazole.

Acknowledgements
The authors gratefully acknowledge the support of the medical records and pharmacy
departments at Concord Repatriation General Hospital, St Vincent’s Hospital, Royal North
Shore Hospital, Royal Prince Alfred Hospital, Westmead Hospital, St George Hospital and
Prince of Wales Hospital. MD is supported by an Australian Postgraduate Award.

Conflicts of Interest
MD, JR, KN, LP, AM: Nothing to declare. SC has been a member of the Antifungal
Advisory Boards of Pfizer Australia, Merck and Gilead Sciences Inc.
References


Figure Legends

**FIGURE 1** Boxplot of relationship between voriconazole daily dose and voriconazole trough concentration.

**FIGURE 2** Receiver Operating Characteristic (ROC) curves for predicting treatment success (Panel A: All treatment patients; Panel B: patients with proven or probable IFI) or neurotoxic adverse events (Panel C) from voriconazole trough concentrations. The true positive rate represents the proportion of true positives that are correctly classified as positive. The false positive rate represents the proportion of true negatives that are incorrectly classified as positive. True positive rate = true positives / (true positives + false negatives); false positive rate = false positives / (false positives + true negatives).
TABLE 1 Patient demographic and clinical characteristics and indications for voriconazole therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of patients (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age (years)</td>
<td>54 (18–88)</td>
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<tr>
<td>Sex, male:female</td>
<td>116 : 85</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 (38–113)</td>
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<tr>
<td><strong>Indication for therapy</strong></td>
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<td>Proven IFI</td>
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<tr>
<td><strong>Underlying condition</strong></td>
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<tr>
<td>None</td>
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<td><strong>Site of infection</strong></td>
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<td>Brain</td>
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<td>Unknown</td>
<td>20</td>
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</table>

*Median (range). Weight available for 187/201 patients. Defined according to the 2008 EORTC/MSG guidelines (8). Fungal cellulitis (6 patients), localized eye infection (5 patients), ear infection (4 patients), esophagitis (2 patients). Chronic lung disease (3 patients), aplastic anemia (2 patients), IgG deficiency (1 patient), severe combined immunodeficiency (1 patient), HIV (1 patient), rheumatoid arthritis (1 patient), systemic lupus erythematosus (1 patient), sarcoidosis (1 patient), scleroderma, caroli syndrome (1 patient), myasthenia gravis (1 patient), ulcerative colitis (1 patient), long-term corticosteroid use (1 patient), intravenous drug use (1 patient), recent brain surgery (1 patient). Does not include patients taking voriconazole for antifungal prophylaxis. Skin and soft tissue involvement (4 patients). Disseminated infection in 4 patients. Lung involvement (1 patient). Lung involvement (1 patient). Endocarditis (2 patients), Liver (2 patients), Bloodstream (2 patients), Esophagitis (2 patients), Osteomyelitis (1 patient).
TABLE 2 Incidence of treatment failure and visual or auditory hallucinations below and above voriconazole concentration limits identified from ROC analysis.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Proposed concentration cutoff</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Treatment Failure</td>
<td>&lt;1.7 mg/L</td>
<td>≥1.7 mg/L</td>
</tr>
<tr>
<td>All treatment patients (n=163)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19/74 (26%)</td>
<td>6/89 (7%)</td>
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<tr>
<td>Proven or probable IFI (n=67)</td>
<td>12/34 (35%)</td>
<td>2/33 (6%)</td>
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<tr>
<td>Visual/auditory hallucinations</td>
<td>≤5 mg/L</td>
<td>&gt;5 mg/L</td>
</tr>
<tr>
<td>All patients (n=201)</td>
<td>2/170 (1.2%)</td>
<td>10/31 (32%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Fisher’s exact or chi-squared test as appropriate. <sup>b</sup> All patients receiving voriconazole for treatment of a known or suspected fungal infection (n=170); treatment outcome evaluable in 163/170 patients.
<table>
<thead>
<tr>
<th>Model term</th>
<th>Coefficient</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Oral administration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−1.348</td>
<td>−1.741 −0.955</td>
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<tr>
<td>Age (years)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.026</td>
<td>0.017 −0.036</td>
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<td>Weight (kg)</td>
<td>−0.028</td>
<td>−0.038 −0.018</td>
<td>&lt;0.01</td>
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<td>Daily dose (mg)</td>
<td>0.005</td>
<td>0.003 −0.006</td>
<td>&lt;0.01</td>
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<td>Concomitant CYP2C19 Inducer&lt;sup&gt;c&lt;/sup&gt;</td>
<td>−2.367</td>
<td>−3.181 −1.553</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Concomitant Prednisone / Prednisolone</td>
<td>−1.012</td>
<td>−1.346 −0.678</td>
<td>&lt;0.01</td>
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<tr>
<td>Concomitant Methylprednisolone</td>
<td>−1.833</td>
<td>−2.445 −1.221</td>
<td>&lt;0.01</td>
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<tr>
<td>Concomitant Dexamethasone</td>
<td>−1.245</td>
<td>−1.991 −0.500</td>
<td>&lt;0.01</td>
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<td>Concomitant Omeprazole</td>
<td>1.141</td>
<td>0.575 −1.706</td>
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<td>Concomitant Pantoprazole</td>
<td>0.685</td>
<td>0.330 −1.041</td>
<td>&lt;0.01</td>
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<tr>
<td>Concomitant Esomeprazole</td>
<td>1.009</td>
<td>0.192 −1.826</td>
<td>&lt;0.05</td>
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<tr>
<td>Concomitant Rabeprazole</td>
<td>1.414</td>
<td>0.800 2.028</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

R<sup>2</sup>=0.24 n=736 concentration measurements. <sup>a</sup> Compared to intravenous administration. <sup>b</sup> Age at time of first voriconazole concentration measurement. <sup>c</sup> Phenytoin or Rifampicin.
**TABLE 4** Univariate analysis of the effect of glucocorticoid co-administration on voriconazole concentration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Voriconazole concentration (mg/L)(^a) when parameter:</th>
<th>p-value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Concomitant Prednisone or Prednisolone</td>
<td>1.25 (2.2)</td>
<td>1.60 (3.1)</td>
</tr>
<tr>
<td>Concomitant Methylprednisolone</td>
<td>1.00 (1.5)</td>
<td>1.50 (2.8)</td>
</tr>
<tr>
<td>Concomitant Dexamethasone</td>
<td>0.40 (1.2)</td>
<td>1.50 (2.8)</td>
</tr>
</tbody>
</table>

\(^a\) Median (Interquartile range). \(^b\) Mann-Whitney U test.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Indication for voriconazole</th>
<th>Lower concentration limit (mg/L)</th>
<th>Upper concentration limit (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troke et al (31)</td>
<td>401 (NR)</td>
<td>Treatment</td>
<td>≥2 (trough/MIC)</td>
<td>≤5 (trough/MIC)</td>
</tr>
<tr>
<td>Present study</td>
<td>201± (7)</td>
<td>Treatment</td>
<td>≥1.7</td>
<td>≤5</td>
</tr>
<tr>
<td>Pascual et al (22)</td>
<td>52 (1)</td>
<td>Treatment</td>
<td>&gt;1</td>
<td>≤5.5</td>
</tr>
<tr>
<td>Neely et al (21)</td>
<td>46 (1)</td>
<td>Treatment</td>
<td>&gt;1</td>
<td>NR</td>
</tr>
<tr>
<td>Ueda et al (32)</td>
<td>34 (1)</td>
<td>Treatment</td>
<td>&gt;2</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Smith et al (25)</td>
<td>28 (1)</td>
<td>Treatment</td>
<td>&gt;2.05&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
</tr>
<tr>
<td>Imhof et al (14)</td>
<td>26 (1)</td>
<td>Treatment</td>
<td>NR</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Miyakis et al (19)</td>
<td>25 (1)</td>
<td>Treatment</td>
<td>&gt;2.2</td>
<td>NR</td>
</tr>
<tr>
<td>Mitsani et al (18)</td>
<td>93 (1)</td>
<td>Prophylaxis</td>
<td>&gt;1.5</td>
<td>NR</td>
</tr>
<tr>
<td>Trifilio et al (30)</td>
<td>71 (1)</td>
<td>Prophylaxis</td>
<td>&gt;2</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported. * Number of patients (number of hospitals). " This limit was based on an association between reduced treatment response rates above 5 mg/L, no association with toxicity was observed. " n=201 for upper concentration limit (toxicity); patients receiving voriconazole for prophylaxis not included in assessment of the lower concentration limit (n=170). " This recommendation was based on randomly timed voriconazole samples, rather than trough sampling.
A

True positive rate

1.0

0.8

0.6

0.4

0.2

0.0

1.7 mg/L

AUC 0.66

95% CI 0.54-0.76, p<0.05

False positive rate

0.0

0.2

0.4

0.6

0.8

1.0

B

True positive rate

1.0

0.8

0.6

0.4

0.2

0.0

1.7 mg/L

AUC 0.72

95% CI 0.56-0.87, p<0.05

False positive rate

0.0

0.2

0.4

0.6

0.8

1.0

C

True positive rate

1.0

0.8

0.6

0.4

0.2

0.0

5 mg/L

AUC 0.92

95% CI 0.87-0.97, p<0.001

False positive rate

0.0

0.2

0.4

0.6

0.8

1.0