Evaluation of the effect of obesity on voriconazole serum concentrations

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Objectives: Voriconazole is a second-generation triazole antifungal, approved by the FDA in 2002. Despite a decade of experience with voriconazole, there are limited published data analysing serum concentrations and toxicity in obese patients. Therefore, we evaluated voriconazole trough serum concentrations in obese and normal-weight patients in a retrospective cohort study.

Methods: Voriconazole serum trough concentrations and toxicities were compared for obese (body mass index ≥ 35 kg/m²) versus normal-weight (body mass index 18.5–24.9 kg/m²) patients receiving 4 mg/kg voriconazole every 12 h.

Results: The obese group (n = 21) had significantly higher mean serum voriconazole trough concentrations than the normal-weight group (n = 66) (6.2 and 3.5 mg/L, respectively, P < 0.0001). Patients in the obese group also had higher rates of supratherapeutic voriconazole levels (>5.5 mg/L) than patients in the normal-weight group (67% versus 17%, respectively, P < 0.0001). However, hepatotoxicity and neurotoxicity rates did not differ between groups. The secondary endpoint compared mean serum voriconazole concentrations in the obese population when dosed at 4 mg/kg based on ideal body weight, adjusted body weight and actual body weight, which were statistically significantly different at 3.95, 3.3 and 6.2 mg/L, respectively (P = 0.0009). Therapeutic voriconazole concentrations (2.0–5.5 mg/L) occurred in 29% of obese patients when dosed on actual body weight, and 45% and 80% of patients when dosed on ideal body weight and adjusted body weight, respectively.

Conclusions: Our results suggest a strong association between supratherapeutic concentrations and morbidly obese patients when dosed at 4 mg/kg actual body weight. Dosing voriconazole based on an ideal body weight or adjusted body weight may be appropriate for morbidly obese patients.

Keywords: dosing, ideal body weight, adjusted body weight, toxicity

Introduction

Although obesity is a growing global pandemic, obese patients are frequently not included in pre-market drug investigations, and are often excluded.1 This practice has led to a void in pharmacokinetic and pharmacodynamic data, as well as appropriate medication dosing recommendations for obese individuals.

Voriconazole is a second-generation triazole antifungal used in the treatment of multiple infections, including invasive aspergillosis, and as antifungal prophylaxis in immunocompromised individuals.2 Voriconazole has a narrow therapeutic index,3,4 and in order to maximize efficacy and minimize toxicity, healthcare providers routinely monitor voriconazole concentrations.2,5 There is a documented lack of response to voriconazole therapy at concentrations <1 mg/L and toxicities, such as hallucinations and encephalopathy, are common at concentrations >5.5 mg/L.2 In a study by Kim et al.,6 a trough concentration ≥5.83 mg/L was determined to be the only independent risk factor identified through multivariate analysis for severe adverse events from voriconazole. The probability of neurotoxicity at concentrations >8 mg/L approaches 90%.7 Due to the non-linear pharmacokinetics of voriconazole, both interindividual and intraindividual variation of voriconazole concentrations can be substantial.8 This phenomenon is often attributed to hepatic enzyme polymorphisms and altered gene expression of CYP2C19.5 It has proven difficult for clinicians to
predict voriconazole plasma concentrations based on the dosage regimen alone.\textsuperscript{6,9,10} Therefore, many authorities recommend obtaining a trough concentration once voriconazole reaches steady-state, with an ideal trough level ranging from 2 to 5.5 mg/L; although the exact therapeutic range has yet to be established.\textsuperscript{2,5} Troke \textit{et al.}\textsuperscript{11} performed an analysis on 825 patients with measured voriconazole concentrations and recorded clinical response. Maximal clinical response was observed in patients with a mean voriconazole concentration of 3.0–4.0 mg/L. They also identified a therapeutic trough/MIC ratio of 2.0–5.0 for patients with an established MIC for isolated organisms.\textsuperscript{11}

Voriconazole is available in both intravenous (iv) and oral formulations, with an estimated oral bioavailability of 96%.\textsuperscript{12} The package insert recommends weight-based dosing of 3–6 mg/kg for iv voriconazole, while recommending a fixed oral dose (200 mg twice daily) for all patients >40 kg.\textsuperscript{12} This dosing recommendation results in similar doses for normal-weight patients between the oral and iv formulations, but a large discrepancy in doses between oral and iv formulations in morbidly obese patients.\textsuperscript{10} An association has been established linking mortality from invasive fungal infections to patients with inappropriate initial trough concentrations, solidifying the need for appropriate initial voriconazole dosing.\textsuperscript{13} Therefore, some practitioners dose both oral and iv voriconazole at 4 mg/kg actual body weight for life-threatening infections.

At this time, it has not been established whether an actual, ideal or adjusted weight should be utilized for obese patients receiving initial voriconazole therapy. The primary purpose of this study was to analyse voriconazole levels and associated toxicities in morbidly obese and normal-weight patients when dosed at 4 mg/kg actual body weight. A secondary analysis compared voriconazole levels in morbidly obese patients dosed at 4 mg/kg based on actual body weight, ideal body weight and adjusted body weight.

\textbf{Patients and methods}

\textbf{Patients}

A retrospective, cohort study was conducted at the University of Michigan Hospitals and Health System. This study was approved by the University of Michigan Investigational Review Board (HUM00053491). Patients \geq 18 years of age, admitted between 1 January 2005 and 31 December 2011, and with a voriconazole level drawn during their hospitalization were screened for inclusion. Patients were divided into two groups based on the WHO’s body mass index (BMI) classification system.\textsuperscript{1} Patients in obesity classes 2 and 3 (BMI \geq 35 kg/m\textsuperscript{2}) served as the treatment group, and normal-weight patients (BMI 18.5–24.9 kg/m\textsuperscript{2}) were used as a control. Patients receiving iv or oral voriconazole at 4 mg/kg, rounded to the nearest 50 mg, were included in the study.

Patients were excluded if taking a medication resulting in a major drug–drug interaction affecting voriconazole concentrations (rifampicin,

\begin{figure}[h]
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\includegraphics[width=\textwidth]{flowダイヤグラム.png}
\caption{Flow diagram. \textsuperscript{a}Primary outcome—comparing obese versus normal-weight patients receiving voriconazole at 4 mg/kg actual body weight. \textsuperscript{b}Secondary outcome—comparing obese patients receiving voriconazole at 4 mg/kg based on ideal body weight, adjusted body weight and actual body weight.}
\end{figure}
rifabutin, high-dose ritonavir, carbamazepine, long-acting barbiturates or St John’s wort). Only the initial voriconazole concentration at treatment dosing was analysed and patients were excluded if the voriconazole dose was adjusted based on previously drawn levels. Voriconazole concentrations drawn within 4 h of administration (iv or oral) were not considered trough concentrations and were excluded from this study. If a loading dose of 6 mg/kg was prescribed, voriconazole was considered to be at steady-state within 24 h and trough concentrations were considered acceptable prior to the second maintenance dose. Without a loading dose, voriconazole trough concentrations were only accepted after the administration of voriconazole for ≥5 days.

### Methods

Patients with an appropriately obtained voriconazole level were separated into two groups: a normal-weight group (BMI 18.5–24.9 kg/m²) and an obese group (BMI ≥35 kg/m²). The primary endpoint included patients dosed at 4 mg/kg actual body weight, in which the mean voriconazole trough was then compared between obese and normal-weight groups. Hepatotoxicity and neurotoxicity rates were also analysed. Hepatotoxicity was defined as any aspartate transaminase (AST) or alanine transaminase (ALT) level more than five times the upper limit of normal. Daily progress notes were screened for documented neurotoxicity.

A secondary endpoint compared mean, subtherapeutic and supratherapeutic voriconazole trough concentrations in the obese group when dosed at 4 mg/kg based on ideal body weight, adjusted body weight and actual body weight. A therapeutic voriconazole level was defined as 2.0–5.5 mg/L. Hepatotoxicity and neurotoxicity were evaluated as part of the secondary endpoint, in a similar way to the primary endpoint. Patient serum samples were analysed by Mayo Medical Laboratories using liquid chromatography–tandem mass spectrometry.

### Statistical analysis

Outcomes were compared using a two-tailed t-test for continuous data and the χ² test for dichotomous data. Secondary outcomes were analysed by a one-way ANOVA with Tukey’s honestly significant difference (‘HSD’) post hoc analysis using SPSS version 19.0.

### Results

A total of 680 patients were screened and 108 met inclusion criteria for utilization of treatment dose voriconazole (Figure 1). There were 21 obese and 66 normal-weight patients receiving voriconazole at 4 mg/kg based on actual body weight. Additionally, 11 obese patients received voriconazole at 4 mg/kg based on ideal body weight and 10 patients received voriconazole based on adjusted body weight. Baseline demographics were generally similar between the groups (Table 1). The majority of patients were Caucasian and diagnosed with a haematological malignancy. Additionally, the majority of patients in each group received oral voriconazole or transitioned from iv to oral

### Table 1. Baseline demographics

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<tr>
<td>Age (years), mean±SD</td>
<td>54.8±15.3</td>
<td>56 ± 12.6</td>
<td>56.3±11.2</td>
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<td>Male, n (%)</td>
<td>40 (61)</td>
<td>13 (62)</td>
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<td>Weight (kg), mean±SD</td>
<td>63.8±10.8</td>
<td>108.7±18.7</td>
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<td>113.2±10.5</td>
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<td>Height (cm), mean±SD</td>
<td>169±11.5</td>
<td>167±13.1</td>
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<td>BMI (kg/m²), mean±SD</td>
<td>22.16±2.0</td>
<td>38.59±5.3</td>
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<td>Voriconazole dose (mg), mean±SD</td>
<td>256.9±4.3</td>
<td>415±74</td>
<td>245.5±52.2</td>
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<td>Voriconazole mg/kg, mean±SD</td>
<td>4.02±0.23</td>
<td>3.91±0.31</td>
<td>4.00±0.19</td>
<td>4.04±0.28</td>
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<td>Patients with voriconazole load, n (%)</td>
<td>30 (45)</td>
<td>18 (86)</td>
<td>4 (36)</td>
<td>7 (70)</td>
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<td>Caucasian</td>
<td>57 (86)</td>
<td>19 (90)</td>
<td>10 (91)</td>
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<td>11 (52)</td>
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<td>16 (24)</td>
<td>8 (38)</td>
<td>2 (18)</td>
<td>5 (50)</td>
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voriconazole prior to obtaining the initial concentration. Although all four groups received 4 mg/kg voriconazole, there were differences noted in the number of patients receiving loading doses and those initiated on oral therapy ($P = 0.0049$ and $P = 0.0126$, respectively).

The average serum voriconazole trough concentration for the obese group was significantly higher than for the normal-weight group (6.2 versus 3.5 mg/L, respectively, $P = 0.0001$) when receiving 4 mg/kg based on actual body weight (Figure 2). Obese patients receiving 4 mg/kg based on actual body weight also had significantly higher rates of supratherapeutic voriconazole concentrations than patients of a normal weight [14 (67%) versus 11 (17%), respectively, $P < 0.0001$] and fewer concentrations within the therapeutic range [6 (29%) versus 33 (50%), respectively, $P = 0.1426$] (Table 2).

The mean serum voriconazole concentrations varied significantly among obese patients, whether dosing of 4 mg/kg was based on ideal body weight, adjusted body weight or actual body weight (Figure 2). The mean voriconazole trough level was 3.95, 3.3 and 6.2 mg/L ($P = 0.0009$) in obese patients when dosed on ideal body weight, adjusted body weight and actual body weight, respectively. Therapeutic voriconazole levels (2.0–5.5 mg/L) were achieved in 6 (29%) obese patients when dosed on actual body weight, and 5 (45%) and 8 (80%) when dosed on ideal body weight and adjusted body weight, respectively.

![Figure 2](https://academic.oup.com/jac/article-fig/67/12/2957/776097)

**Table 2. Comparison of dosing strategies, voriconazole levels and toxicity**

|----------------|-------------------------------------|------------------------------------------|------------------------------------------|-------------------------------------------|-------
| Concentration (mg/L), mean±SD, 95% CI | 3.5±2.86, 2.8–4.2 | 6.2±2.09, 5.3–7.2 | 3.95±2.81, 2.1–5.8 | 3.3±1.32, 2.4–4.2 | 0.0009
| Subtherapeutic (<2 mg/L, n (%))    | 22 (33) | 1 (5) | 3 (27) | 2 (20) | 0.0613
| Therapeutic (2–5.5 mg/L, n (%))    | 33 (50) | 6 (29) | 5 (45) | 8 (80) | 0.0599
| Supratherapeutic (>5.5 mg/L, n (%))| 11 (17) | 14 (67) | 3 (27) | 0 | <0.0001
| Neurotoxicity, n (%)               | 10 (15) | 4 (19) | 2 (18) | 1 (10) | 0.9211
| Liver toxicity, n (%)              | 4 (6) | 1 (5) | 1 (9) | 0 | 0.823

*P value <0.05 for normal-weight patients versus obese patients receiving voriconazole based on actual body weight.
patients dosed on ideal body weight and adjusted body weight, respectively (P = 0.0599) (Table 2). However, numerically higher rates of subtherapeutic levels were found in the ideal body weight and adjusted body weight groups [3 (27%) and 2 (20%), respectively] compared with the actual body weight group [1 (5%), P = 0.1822]. Only three patients (14%) in the ideal or adjusted body weight groups experienced supratherapeutic levels (>5.5 mg/L). Additionally, only one patient in the obese group and four patients in the normal-weight group experienced AST or ALT more than five times the upper limit of normal (P = 0.75), with two of the five patients presenting with a voriconazole trough level > 5.5 mg/L. Neurotoxicity and onset of neurotoxicity, presenting as mental status changes or visual hallucinations, did not differ between the study arms (P = 0.9211). Across all groups, neurotoxicity occurred in 17 patients, with 8 of those correlating to voriconazole trough levels > 5.5 mg/L.

**Discussion**

These data suggest a strong relationship between supratherapeutic voriconazole concentrations and morbidly obese patients receiving 4 mg/kg based on actual body weight, and that dosing based on ideal body weight or adjusted body weight might be appropriate for morbidly obese patients. These results complement and fill a gap with two prior studies that evaluated voriconazole pharmacokinetics in obese patients or volunteers. 14,15

Pai and Lodise14 evaluated voriconazole dosing in eight healthy, obese volunteers stratified by BMI class, receiving a standard 200 or 300 mg, non-weight-adjusted, oral dose. The respective average voriconazole doses for the obese groups were 1.5 and 2.25 mg/kg, well below the recommended treatment dose of a 6 mg/kg load and 4 mg/kg subsequently every 12 h. The mean voriconazole trough levels were 0.81 and 1.76 mg/L for the 200 and 300 mg doses, respectively. These pharmacokinetic values were compared with those of normal-weight patients enrolled in a previously published dose-escalation study.15 This comparison demonstrated obese patients (BMI > 35 kg/m²) experienced higher average serum voriconazole trough levels than non-obese patients (BMI ≤ 30 kg/m²) when dosed at 200 mg twice daily (0.81 versus 0.35 mg/L, respectively), although this was not statistically significant.

Davies-Vorbrodt et al.15 presented an abstract looking at the relationship between voriconazole dose and serum concentration in obese patients. Ninety-two patients were evaluated and stratified based on BMI. The authors demonstrated statistically significantly higher mean voriconazole concentrations in patients weighing > 80 kg and in those with a BMI > 25 kg/m². However, it was unclear what dosing strategy was utilized for patients in this study and it was not stated if confounders, such as drug–drug interactions, were controlled for or if voriconazole levels were appropriately obtained.

This analysis reports mean voriconazole trough levels of 3.95 and 3.3 mg/L, falling within the therapeutic window when obese patients were dosed at 4 mg/kg ideal body weight and adjusted body weight, respectively. However, the rates of subtherapeutic concentrations (<2.0 mg/L) were higher, but not statistically different, for patients dosed on ideal or adjusted body weight [3 (27%) and 2 (20%), respectively] compared with actual body weight [1 (5%), P = 0.1882]. Unfortunately, due to the study design and sample size it cannot be concluded if an ideal body weight or an adjusted body weight is optimal for voriconazole dosing in obese patients, and further study is needed. Additionally, the range of voriconazole serum concentrations was fairly large among all groups (0.1–14 mg/L), which supports the need for therapeutic drug monitoring and individualized dose adjustment.

Although our results suggest a strong association between supratherapeutic concentrations and morbidly obese patients receiving voriconazole at 4 mg/kg actual body weight, toxicity differences were not observed. There are several possible explanations, including a small sample size, limits of the study design and potentially different toxicity parameters in morbidly obese patients. There is a strong association with neurotoxicity and elevated voriconazole trough levels in the existing literature, with symptoms occurring within the first few days of initiating therapy.16 Therefore, our study design may have excluded some patients experiencing neurotoxicity if voriconazole was discontinued prior to obtaining a voriconazole level.

As with any retrospective analysis, there are inherent limitations to our study. We controlled for potential confounding factors that could affect voriconazole levels as much as possible; excluding patients with drug–drug interactions, levels drawn prior to steady-state and levels not considered a trough. Other confounding factors, including the amount of high-fat food consumed and genetic polymorphisms of the cytochrome system, could not be assessed in this retrospective review.

Our results showed significantly higher rates of supratherapeutic voriconazole levels when obese patients were dosed at 4 mg/kg actual body weight. However, neurotoxicity and hepatotoxicity were similar between the groups. Practitioners could consider initial voriconazole dosing utilizing ideal body weight or adjusted body weight for morbidly obese patients, with dose adjustment following voriconazole serum monitoring. Further studies are required to characterize the appropriate voriconazole dosing strategy in morbidly obese patients and corresponding toxicity rates.

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**Transparency declarations**

None to declare.

**References**