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Pharmacokinetics of Intravenous Voriconazole in Obese Patients: Implications of CYP2C19 Homozygous Poor Metabolizer Genotype

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Abstract

There is a paucity of pharmacokinetic studies describing weight-based dosing of intravenous (IV) voriconazole in obesity. We report the pharmacokinetics of IV voriconazole in an obese CYP2C19 homozygous poor metabolizer and review previously reported data of IV voriconazole in obesity. A 17-year-old obese Hispanic male (BMI=35 kg/m^2) received IV voriconazole for treatment of suspected aspergillosis. After 2.5 days of voriconazole 4 mg/kg IV every 12 hours using adjusted body weight, the voriconazole area under the serum concentration versus time curve over the course of a single dosing interval ($AUC_{0–12}$) and trough concentration were 86,100 ng•h/ml and 6.2 mcg/ml, respectively. The voriconazole dosage was then decreased. A trough concentration drawn just before dose reduction (after 8.5 days of voriconazole 4 mg/kg IV every 12 hours) remained elevated (5.8 mcg/ml). Genotyping revealed a CYP2C19 homozygous poor metabolizer (*CYP2C19*2/*2*). Voriconazole was subsequently discontinued due to QTc prolongation. These data and two recent publications suggest that voriconazole does not distribute extensively into human adipose tissue and that obese patients should be dosed on an adjusted weight basis. If an obese patient dosed on total body weight is also a CYP2C19 poor metabolizer, serum voriconazole concentrations will be further elevated, potentially leading to drug-induced toxicity.

Keywords

voriconazole; obese; intravenous; CYP2C19; pharmacokinetics

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Introduction

The epidemic of obesity in children and adults presents challenges when dosing antimicrobial agents for the treatment of life-threatening infections.[1–3] Pai and colleagues recently reported the pharmacokinetics of fixed dose oral voriconazole in obese patients.[4] However, there is a paucity of pharmacokinetic studies describing weight-based dosing of intravenous voriconazole in obesity.[5,6] To our knowledge, only two cases of obese patients receiving intravenous voriconazole have been reported.[5,7] Furthermore, the effect of obesity on voriconazole dosing has not been extensively studied in patients with genetic polymorphisms in CYP2C19,[7] which is the principle enzyme involved in voriconazole metabolism. Herein we report the pharmacokinetics of intravenous voriconazole in an obese patient and review the data from previously reported cases in order to provide guidance in the management of dosing such patients.

Case Report

A 17-year-old Hispanic male with chemotherapy refractory pre-B acute lymphoblastic leukemia was referred for treatment on a Phase I trial of an anti-CD22 immunotoxin (Clinicaltrials.gov identifier NCT 00659425). The patient's underlying conditions included obesity with a body mass index (BMI) of 35 kg/m^2 (height 170.9 cm, weight 102.1 kg), history of Aspergillus infection of the nasal septum and presumed pulmonary aspergillosis, neutropenia, and diabetes mellitus. Computed tomography showed an enlarging right middle lobe pulmonary nodule which prompted the initiation of intravenous voriconazole 500 mg (4.9 mg/kg) IV every 12 hours × 2 doses, then 420 mg (4.1 mg/kg) IV every 12 hours for 4 days based on the total body weight (TBW) of 102.1 kg. As the patient had a previous history of immunotoxin-related liver dysfunction, he was considered to be at increased risk for voriconazole-related hepatotoxicity. A rise in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) prompted consultation with the Clinical Pharmacy Service and the voriconazole dose was then decreased to 340 mg IV every 12 hours using an adjusted body weight (ABW) of 85 kg (4 mg/kg ABW). The patient was not receiving any medications known to alter voriconazole metabolism.

Due to limited information on voriconazole pharmacokinetics in obese patients, serum voriconazole concentrations were collected in an effort to inform further dosing adjustments. Serum concentrations were determined by liquid chromatography-tandem mass spectrometry assay at the Mayo Medical Laboratories, Rochester, MN. Voriconazole pharmacokinetics were determined using standard noncompartmental methods with the WinNonlin® Professional computer program (version 5.0, Pharsight Corporation, Mountain View, CA).

Voriconazole pharmacokinetic parameters after 2.5 days of dosing according to ABW (340 mg IV every 12 hours) are presented in Table 1. The voriconazole area under the serum concentration versus time curve over the course of a single dosing interval ($AUC_{0–12}$) and trough concentration (C_{min}) were 86,100 ng•h/ml and 6.2 mcg/ml, respectively. These values are 2 to 3 fold higher than target values for $AUC_{0–12}$ and C_{min}, which are 42,000 ng•h/ml and 1.0 to 2.0 mcg/ml, respectively.[8] The voriconazole dose was then decreased to 280 mg IV every 12 hours. The patient's trough concentration drawn before the dose reduction (after receiving 8.5 days of voriconzole 340 mg IV every 12 hours) remained elevated at 5.8 mcg/ml. Based upon excessive values for $AUC_{0–12}$ and C_{min} and the prolonged voriconazole half-life and reduced clearance (Table 1), CYP2C19 genotyping was performed (Medical Oncology Branch Center for Cancer Research, NCI, NIH, Bethesda, MD). The patient's genotype was *CYP2C19*2/*2*, a homozygous poor metabolizer. During treatment with voriconazole, the patient's pulmonary nodule remained stable. Following

reduction of the voriconazole dosage, the serum ALT continued to decline and the serum alkaline phosphatase remained stable. However, six days after the voriconazole dose reduction the serum AST increased in association with proliferation of leukemic blast cells. Voriconazole was subsequently discontinued due to QTc prolongation possibly related to electrolyte abnormalities and elevated voriconazole concentrations. No other clinically significant toxicities were apparent despite the increased systemic exposure of voriconazole. The patient was transferred to a medical center near his home for further decisions in management of his cancer and invasive fungal infection.

Discussion

The magnitude of elevated body weight and CYP2C19 genotype are two key factors to consider when dosing intravenous voriconazole in obese patients. While the distribution of voriconazole in adipose tissue in animals and humans is unknown, two recent publications suggest that voriconazole may not distribute extensively into fat tissue in humans.[4,5] Dickmeyer and colleagues reported a patient with a BMI of 84.5 kg/m^2 who received voriconazole 4 mg/kg IV every 12 hours based on an ABW, which achieved an AUC of 41,850 ng•h/ml (Table 1).[5] The authors suggest that using ABW in obese patients may achieve AUC values similar to those observed in non-obese patients. Furthermore, Pai and colleagues found that voriconazole AUCs were comparable between obese and non-obese patients receiving a fixed oral dose of 200 mg or of 300 mg every 12 hours.[4] These findings suggest that voriconazole distributes primarily into lean body tissue with a smaller distribution into adipose tissue. The correlation (r^2) of voriconazole dose normalized $AUC_{0–12}$ and TBW, IBW, ABW, and lean body weight were 0.14, 0.31, 0.38, and 0.42, respectively. The authors recommended that TBW should not be used for dosing oral or intravenous voriconazole in obese patients.

If obese patients are dosed with intravenous voriconazole on a weight basis (mg/kg) using TBW, voriconazole concentrations may be elevated. Based on its chemical properties, it is logical to presume that voriconazole preferentially distributes to lean body tissues as opposed to adipose tissue and therefore should not be dosed based on TBW. Voriconazole, along with fluconazole belongs to a class of hydrophilic triazoles. These compounds contain an isopropyl core with substitutions at carbons 1, 2, and 3. These hydrophilic triazoles differ structurally from the hydrophobic triazoles, such itraconazole and posaconazole, by the absence of a chain of aromatic and aliphatic substitutions on the asymmetric carbon atom. The chemical structure of voriconazole would predict reduced distribution into adipose tissue in comparison to that of plasma. In a manner similar to adjustment for reduced aminoglycoside distribution into adipose tissue, several formulas may be used for ABW. Formulas for ABW such as IBW + 0.3(TBW - IBW) and IBW + 0.4 (TBW - IBW) have been proposed for voriconazole dosing in obese patients (Table 1).[5,7]

The effect of CYP2C19 polymorphisms on voriconazole pharmacokinetics has been extensively described.[9–12] However, CYP2C19 genotyping was not performed in the majority of reports on voriconazole pharmacokinetics in obesity.[4,5] This case and our earlier case report[7] highlight the altered pharmacokinetic properties of intravenously administered voriconazole in obese patients with the CYP2C19 homozygous poor metabolizer genotype (Table 1). As illustrated herein and elsewhere[7], using TBW in obese CYP2C19 homozygous poor metabolizers will likely lead to very high voriconazole concentrations. Even when using ABW, the two obese CYP2C19 poor metabolizers encountered in our practice still had excessively elevated AUC's. This is consistent with the conclusion of Lee et al. that CYP2C19 poor metabolizers have approximately three fold higher voriconazole exposure when a standard fixed oral dose of voriconazole is administered to non-obese healthy volunteers.[9] Thus, the presence of persistently elevated serum concentrations of

voriconazole in an obese patient, despite dosage adjustment for reduced penetration into adipose tissue, should prompt determination of CYP2C19 genotype for possible poor metabolizer status. The availability of an FDA approved system for determination of CYP2C19 genotype should facilitate this assessment.[13,14]

Recent reports underscore the importance of achieving target trough concentrations of voriconazole > 1 mcg/ml in improving efficacy against invasive aspergillosis as well as the association between toxicity and trough levels > 5 mcg/ml.[15,16] For patients with obesity, achieving target therapeutic concentrations while minimizing toxicity may be more accurately achieved by dosing according to ABW.

In conclusion, obese patients receiving intravenous voriconazole should not be dosed based on TBW. Instead, these individuals should be dosed using ABW augmented by therapeutic drug monitoring to assess the adequacy of voriconazole dosing and to guide dosing adjustments. CYP2C19 genotyping is recommended for patients who display persistently elevated serum concentrations or signs and symptoms of toxicity while already receiving a voriconazole dose based on ABW.

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Table 1

Intravenous Voriconazole Pharmacokinetic Parameters in Three Obese Patients.

Pharmacokinetic Parameter	Case 1 (This Case)	Case 2[7]	Case 3[5]
Age (years)	17	41	30
BMI (kg/m^2)	35	36	84.5
TBW (kg)	102.1	134.5	225
ABW (kg)	85[a]	101.3[b]	Not reported[a]
CYP2C19 genotype	*CYP2C19*2/*2*	*CYP2C19*2/*2*	Not reported
IV voriconazole dosage	4 mg/kg	4 mg/kg	4 mg/kg
IV voriconazole dose (based upon ABW) every 12 hours	340 mg[c]	405 mg[d]	Not reported[e]
AUC_{0-12}(ng•h/ml)	86,100	77,790	41,850
Clearance (L/h)	3.9	5.01	Not reported
Vd (L)	157	221	Not reported
$t_{1/2}$(h)[f]	29.3	30	Not reported
trough (mcg/ml)	6.2	6.1	Not reported

BMI = body mass index; TBW = total body weight; ABW = adjusted body weight; AUC_{0-12} = area under the serum concentration versus time curve over the course of a single dosing interval; Vd = volume of distribution; $t_{1/2}$ = half-life.

[a] ABW = IBW + 0.4 (TBW – IBW)

[b] ABW = IBW + 0.3 (TBW – IBW)

[c] infusion time (1.75 h), collection time points from beginning of infusion (2.75, 5.75, 9.75, 11.75 h).

[d] infusion time (1.75 h); collection time points from beginning of infusion (2.5, 5.6, 9.5, 11.5 h).

[e] infusion time not reported; collection time points from beginning of infusion (1, 5, 9, 12 h).

[f] The elimination rate constant (λ_z) was estimated as the absolute value of the slope of a linear regression of a natural logarithm of concentration versus time using at least 3 points on the line. Half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$.