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CLINICAL THERAPEUTICS

Evaluation of Total Body Weight versus Adjusted Body Weight Voriconazole Dosing in Obese Patients

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ABSTRACT This retrospective single-center study of a cohort of adult patients who received voriconazole with a steady-state trough concentration measured during therapy evaluated the rate of therapeutic trough attainment using adjusted body weight (AdjBW)-based and total body weight (TBW)-based dosing in overweight and obese patients. Of the 130 patients included, 45 patients received TBW-based dosing and 85 patients received AdjBW-based dosing. Therapeutic trough attainment was significantly improved with AdjBW-based dosing compared to TBW-based dosing (64.7% versus 46.7%; $P = 0.047$).

KEYWORDS anti-infection agents, antifungal therapy, azole antifungals, azoles, drug monitoring, fungal infections, obesity, therapeutic drug monitoring, voriconazole

Voriconazole, an expanded-spectrum triazole antifungal, has a narrow therapeutic index, saturable metabolism, variable absorption, and nonlinear kinetics requiring therapeutic drug monitoring (TDM) to ensure safety and efficacy (1–5). Weight-based dosing, calculated with total body weight (TBW), ideal body weight (IBW), or adjusted body weight (AdjBW), is recommended, but there is no standard dosing weight for obese patients (1, 4, 6, 7). Data for obese patients, primarily defined as those with a body mass index (BMI) of ≥35 kg/m^2, have shown associations between TBW-based dosing with supratherapeutic concentrations and AdjBW-based dosing with therapeutic concentrations (8–11).

In 2015, Barnes-Jewish Hospital (BJH) enacted an AdjBW dosing protocol for patients weighing ≥120% of their IBW; this threshold was chosen to be consistent with dosing for other drugs (e.g., aminoglycosides) and with an assumption that AdjBW dosing would be appropriate for overweight and obese patients. The objective of this study was to compare the rate of therapeutic trough attainment between TBW-based and AdjBW-based dosing in patients weighing ≥120% of their IBW.

This retrospective single-center cohort included patients ≥18 years of age weighing ≥120% of their IBW admitted to BJH between 1 August 2009 and 31 May 2018 who received voriconazole with a steady-state trough concentration. Patients with IBW-based dosing, a diagnosis of cirrhosis, total bilirubin levels of >5 times the upper limit of normal, or concomitant medications known to strongly influence voriconazole metabolism were excluded.

Eligible patients were separated into treatment arms based on AdjBW- or TBW-based dosing. The loading and maintenance doses administered were divided by the patient's IBW, TBW, and AdjBW at the time of admission to produce the patient's dose in milligrams per kilogram of body weight. The dosing strategy for each patient was the weight that produced the dose closest to a 6-mg/kg loading dose and 4-mg/kg maintenance dose.

The first trough concentration, defined as a concentration collected 10 to 14 h after a dose, drawn at steady state was used for comparison. Steady state was defined as a

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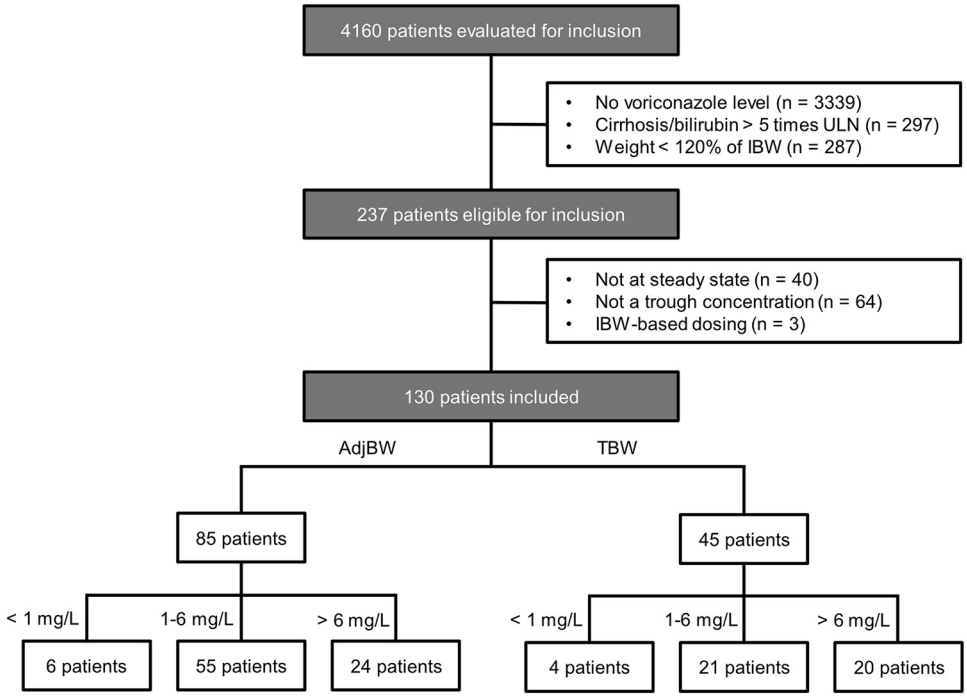

FIG 1 Flow diagram of the patient selection process. "Eligible" refers to patients with at least one voriconazole concentration who met initial inclusion and exclusion criteria. "Included" refers to patients with voriconazole dosed based on total body weight (TBW) or adjusted body weight (AdjBW) with at least one steady-state trough concentration.

trough concentration drawn at least 48 h after the first loading dose if the patient received loading doses of 6 mg/kg every 12 h for two doses or at least 5 days after voriconazole initiation if no loading doses were administered (9–11).

The primary endpoint was the rate of therapeutic trough attainment (1 to 6 mg/liter), using AdjBW-based dosing compared to TBW-based dosing in patients weighing ≥120% of their IBW (1). Secondary outcomes included the rate of subtherapeutic (less than 1 mg/liter) and supratherapeutic (greater than 6 mg/liter) troughs between groups (1). Subgroup analyses were performed to compare outcomes based on the World Health Organization obesity categories (12).

Outcomes were compared using chi-square or Fisher's exact test for nominal data and Student's *t* test or Mann-Whitney U test for continuous data. Statistical significance was defined by a P value of <0.05.

Inclusion criteria were met by 130 of the 821 patients who had a voriconazole trough concentration, including 85 patients in the AdjBW group and 45 patients in the TBW group (Fig. 1). Baseline characteristics were similar between groups, except that patients in the AdjBW group had higher weights (Table 1).

Therapeutic trough attainment was significantly improved with AdjBW-based dosing in patients weighing ≥120% of their IBW (46.7% versus 64.7%, $P = 0.047$) (Fig. 2). The improved rate of therapeutic trough attainment with AdjBW-based dosing was maintained with a similar magnitude of improvement across all BMI subgroups (Table 2).

Patients in the TBW-based group had higher rates of supratherapeutic trough concentrations, although this did not reach statistical significance (44.4% versus 28.2% [$P = 0.063$], respectively). Overall, there was no significant difference in the rate of subtherapeutic trough concentrations (8.9% versus 7.1% [$P = 0.737$], respectively).

These results show improved rates of therapeutic trough attainment and suggest decreased rates of supratherapeutic concentrations with AdjBW-based dosing in patients

TABLE 1 Baseline demographics and voriconazole dosing and level characteristics

Result	Value for patients in dosing group		*P* value
	TBW (*n* = 45)	AdjBW (*n* = 85)	
Age (yrs) [median (IQR)]	61 (44, 70)	62 (52, 70)	0.570
No. (%) of males	20 (44.4)	47 (55.3)	0.239
No. (%) of patients of race			
Caucasian	38 (84.4)	74 (87.1)	0.681
Black	5 (11.1)	8 (9.4)	0.490
Other	2 (4.4)	3 (3.5)	0.567
Ht (in.) (mean ± SD)	66.2 ± 3.53	67.8 ± 3.92	0.180
Wt (kg) [median (IQR)]	87.1 (71.4, 96.7)	96.2 (83.4, 109.1)	0.007
BMI (kg/m^2) [median (IQR)]	30.3 (27.2, 32.7)	31.1 (29.6, 34.5)	0.047
No. (%) with BMI (kg/m^2)			
25–29.9	20 (44.4)	28 (32.9)	0.196
30–34.9	17 (37.8)	40 (47.1)	0.310
≥35	6 (13.3)	16 (18.8)	0.427
No. (%) with underlying immunosuppression[a]			
Hematologic malignancy	16 (35.6)	32 (37.6)	0.814
Bone marrow transplant	10 (22.2)	27 (31.8)	0.251
Solid organ transplant	9 (20.0)	13 (15.3)	0.496
Other	10 (22.2)	13 (15.3)	0.325
No. (%) with i.v. therapy[b]	36 (80.0)	65 (76.5)	0.765
No. (%) with dosing strategy			
Loaded	39 (86.7)	70 (82.4)	0.525
Not loaded	6 (13.3)	15 (17.6)	0.525
Loading dose [median (IQR)]			
In mg	526 (470, 600)	464 (400, 500)	0.012
In mg/kg[c]	5.8 (5.6, 6.0)	5.9 (5.7, 6.1)	0.089
Maintenance dose [median (IQR)]			
In mg	335 (300, 365)	313 (250, 350)	0.123
In mg/kg[c]	3.9 (3.5, 4.1)	3.9 (3.7, 4.2)	0.098
Voriconazole trough (mg/liter) [median (IQR)]	4.9 (2.2, 7.4)	4.6 (2.5, 6.7)	0.632
Time to trough attainment (days)[d] [median (IQR)]			
Loaded	6.0 (3.9, 13.8)	5.6 (3.4, 7.9)	0.679
Not loaded	5.9 (5.5, 8.6)	10.5 (7.5, 19)	0.014

[a]Hematologic malignancy refers to patients who had not undergone a bone marrow transplant prior to voriconazole initiation. Bone marrow transplant refers to patients with or without a hematologic malignancy who had undergone a bone marrow transplant prior to voriconazole initiation.
[b]Patients receiving intravenous (i.v.) therapy at the time of voriconazole trough concentration.
[c]Respective dosing weight per treatment group was utilized to calculate the dose in milligrams per kilogram.
[d]Time to the first voriconazole concentration obtained during the study period.

weighing ≥120% of their IBW, which complement and supplement the previous literature with the inclusion of both overweight and obese patients (9–11).

While previous literature showed that AdjBW leads to more appropriate voriconazole dosing, data were limited by small population sizes, narrow definitions of obesity, use of random voriconazole concentrations, and variable definitions of steady-state concentrations, necessitating further study. Although one may assume that only patients at the upper extremes of BMI would benefit from AdjBW-based dosing, this study demonstrates a benefit despite a broader definition of obesity.

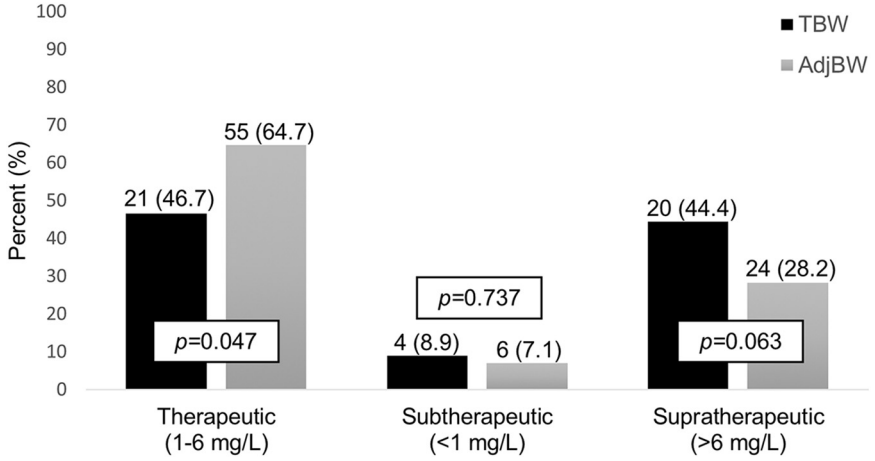

FIG 2 Rate of therapeutic, subtherapeutic, and supratherapeutic trough concentrations in the total population. Data are numbers (percentages) of patients with therapeutic, subtherapeutic, and supratherapeutic trough concentrations.

Our results suggest an association between TBW-based dosing and supratherapeutic concentrations in all subgroups, but statistical significance was seen only in patients with a BMI of 25 to 29.9 kg/m^2. The inability to show a significant difference in the overall rate is likely the result of small sample size.

There was no significant difference in the rate of subtherapeutic concentrations. Four of the six patients in the AdjBW-based group with subtherapeutic concentrations (ranging between 0.5 and 0.9 mg/liter) had therapeutic levels following dose increases. One patient was transitioned to isavuconazole and one patient was transitioned to posaconazole with therapeutic levels during therapy. Overall, these results suggest that AdjBW-based dosing improves therapeutic trough attainment without increasing the risk of subtherapeutic concentrations.

This study increases the generalizability of AdjBW-based dosing through the inclusion of overweight and obese patients weighing ≥120% of their IBW. Confounding factors were also limited by strictly defining trough concentrations and time to steady state. Due to the retrospective design, some factors could not be assessed, including genetic hepatic enzyme polymorphisms and rationale for trough concentrations. Additionally, this study had a low rate of trough attainment, which may have led to

TABLE 2 Primary and secondary outcomes

Outcome	No. (%) of patients in dosing group		*P* value
	TBW (*n* = 45)	AdjBW (*n* = 85)	
Primary outcome			
Therapeutic trough attainment	21 (46.7)	55 (64.7)	0.047
BMI, 25–29.9 kg/m^2	10/20 (50.0)	20/28 (71.4)	0.131
BMI, 30–34.9 kg/m^2	8/17 (47.1)	26/40 (65.0)	0.207
BMI, ≥35 kg/m^2	2/6 (33.3)	8/16 (50.0)	0.417
Secondary outcomes			
Subtherapeutic trough attainment	4 (8.9)	6 (7.1)	0.737
BMI, 25–29.9 kg/m^2	1/20 (5.0)	4/28 (14.3)	0.297
BMI, 30–34.9 kg/m^2	2/17 (11.8)	1/40 (2.5)	0.209
BMI, ≥35 kg/m^2	1/6 (16.7)	1/16 (6.3)	0.481
Supratherapeutic trough attainment	20 (44.4)	24 (28.2)	0.063
BMI, 25–29.9 kg/m^2	9/20 (45.0)	4/28 (14.3)	0.018
BMI, 30–34.9 kg/m^2	7/17 (41.2)	13/40 (32.5)	0.530
BMI, ≥35 kg/m^2	3/6 (50.0)	7/16 (43.8)	0.583
Trough concn of 1–2 mg/liter	6 (13.3)	14 (16.5)	0.637

selection bias. Although it resulted in a high number of excluded patients, the low rate of trough attainment can be explained by patients receiving prophylactic dosing, patients receiving empirical short-term treatment, and patients admitted on established therapeutic regimens, which would limit the clinical utility of TDM.

In this study, AdjBW-based voriconazole dosing significantly improved rates of therapeutic trough attainment compared to TBW-based dosing in patients weighing ≥120% of their IBW. Increased rates of supratherapeutic trough concentrations were associated with TBW-based dosing. Based on the results of this study and previous literature, AdjBW-based voriconazole dosing, combined with TDM, should be strongly considered in patients weighing ≥120% of their IBW.

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