Title

Low Rates of Antifungal Therapeutic Drug Monitoring Among Inpatients Who Received Itraconazole, Posaconazole, or Voriconazole, United States, 2019-2021.

Journal

Open Forum Infectious Diseases, 10(8)

ISSN

2328-8957

Authors

Benedict, Kaitlin
Gold, Jeremy
Toda, Mitsuru
et al.

Publication Date

2023-08-01

DOI

10.1093/ofid/ofad389

Peer reviewed

Open Forum Infectious Diseases

BRIEF REPORT

Low Rates of Antifungal Therapeutic Drug Monitoring Among Inpatients Who Received Itraconazole, Posaconazole, or Voriconazole, United States, 2019–2021

Kaitlin Benedict,[1] Jeremy A. W. Gold,[1] Mitsuru Toda,[1] George R. Thompson III,[2,3] Nathan P. Wiederhold,[4] and Dallas J. Smith[1,5]

[1]Mycotic Diseases Branch, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [2]Department of Internal Medicine, Division of Infectious Diseases, University of California, Davis Medical Center, Sacramento, California, USA, [3]Department of Medical Microbiology and Immunology, University of California, Davis, California, USA, [4]Fungus Testing Laboratory, Department of Pathology and Laboratory Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA, and [5]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Antifungal therapeutic drug monitoring (TDM) is recommended for hospitalized patients receiving itraconazole, posaconazole, or voriconazole for treatment or prophylaxis. In this analysis of hospital-based data, TDM was uncommonly performed (15.8%) in a large cohort of eligible patients, suggesting missed opportunities to avoid subtherapeutic drug levels and minimize toxicity.

Keywords. drug monitoring; itraconazole; posaconazole; United States; voriconazole.

The Infectious Diseases Society of America recommends antifungal therapeutic drug monitoring (TDM) for certain patients, including those receiving azole therapy for invasive aspergillosis, coccidioidomycosis, blastomycosis, or histoplasmosis; prolonged azole prophylaxis; or treatments with potential drug interactions with azoles [1, 2]. Itraconazole, posaconazole, and voriconazole have narrow therapeutic indices, variable pharmacokinetic profiles, and frequent drug–drug interactions [2, 3]. TDM for these antifungals is particularly important in patients prone to unpredictable drug levels such as pediatric patients, those with critical illness, and those with impaired absorption, obesity, or kidney or liver dysfunction [2, 3].

Received 19 May 2023; editorial decision 17 July 2023; accepted 19 July 2023; published online 20 July 2023

Correspondence: Kaitlin Benedict, MPH, Mycotic Diseases Branch, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS H24-9, Atlanta, GA 30329, USA (jsy8@cdc.gov); Dallas J. Smith, Mycotic Diseases Branch, Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS H24-9, Atlanta, GA 30329, USA (rhq8@cdc.gov).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofad389

TDM may improve clinical outcomes by minimizing toxicity associated with supratherapeutic serum drug levels, avoiding treatment failure due to suboptimal drug levels, and potentially preventing antifungal resistance [3, 4]. However, a recent study of patients receiving systemic triazoles for invasive fungal infections at 55 medical centers showed that TDM was uncommon (performed for only 41% of eligible patients) [5]. Other real-world data about TDM use in the United States (US) are scarce. Additional information could help identify factors associated with and barriers to TDM use. Therefore, we analyzed a large hospital-based database to describe TDM use among inpatients receiving itraconazole, posaconazole, or voriconazole during 1 January 2019–31 December 2021.

METHODS

We used the 2019–2021 PINC-A1 Healthcare Database (PHD), a hospital-based all-payer database that contains healthcare utilization, financial, and pharmacy data from >1000 US hospitals; laboratory data (encompassing both in-house and send-out testing) are available from a subset (~25%) of hospitals [6]. We defined antifungal TDM-eligible hospitalizations as those in which inpatients received itraconazole for ≥5 days, posaconazole for ≥5 days, or voriconazole for ≥3 days [3]. No hospitalizations in the dataset had isavuconazole or fluconazole TDM. We limited the main analysis to antifungal TDM-eligible hospitalizations from hospitals and months in which the hospital reported at least 1 TDM test to PHD during that month. We identified underlying conditions and complications using *International Classification of Diseases, Tenth Revision* (*ICD-10*) discharge diagnosis codes (Supplementary Table 1). We described features (eg, demographic characteristics, underlying conditions and complications, outcomes, hospital features) of antifungal TDM-eligible hospitalizations and compared those in which patients did and did not receive TDM, using χ^2, Fisher exact, and Wilcoxon tests ($\alpha = .05$). We also described TDM timing and results by drug and dosage form.

RESULTS

Among 2623 antifungal TDM-eligible hospitalizations from hospitals with TDM data available, TDM was performed during 414 (15.8%) hospitalizations at 50 hospitals (Table 1). Ten of those hospitals contributed 68% of the hospitalizations in which TDM was performed.

By antifungal drug, TDM use was 28.6% for itraconazole (68.1% of which also had hydroxyitraconazole TDM testing), 5.7% for posaconazole, and 17.9% for voriconazole. Among all hospitalizations in which TDM was performed, 277

Table 1. Hospitalizations Among Patients Who Received Itraconazole, Posaconazole, or Voriconazole, by Use of Antifungal Therapeutic Drug Monitoring, 2019–2021

Characteristic	Total (N = 2623)	TDM Performed (n = 414)	TDM Not Performed (n = 2209)	*P* Value
Demographic and hospitalization features				
Age, y, median (IQR)	59.0 (45–68)	58.0 (42–68)	60.0 (46–68)	.454
Age category, y				.119
<18	79 (3.0)	19 (4.6)	60 (2.7)	
18–64	1631 (62.2)	251 (60.6)	1380 (62.4)	
≥65	913 (34.8)	144 (34.8)	769 (34.8)	
Sex				.220
Male	1557 (59.4)	257 (62.1)	1300 (58.9)	
Female	1066 (40.6)	157 (37.9)	909 (41.2)	
Race/ethnicity (n = 2451)				.083
Hispanic	215 (8.7)	27 (7.2)	188 (9.1)	
Non-Hispanic White	1703 (69.5)	257 (68.7)	1446 (69.6)	
Non-Hispanic Black	397 (16.2)	62 (16.6)	335 (16.1)	
Non-Hispanic Asian	59 (2.4)	[a]	[a]	
Non-Hispanic other race	77 (3.1)	20 (5.3)	57 (2.7)	
Payer				.272
Medicare	1150 (43.8)	183 (44.2)	967 (43.8)	
Private health insurance	958 (36.5)	139 (33.6)	819 (37.1)	
Medicaid	363 (13.8)	61 (14.7)	302 (13.7)	
Other	152 (5.8)	31 (7.5)	121 (5.5)	
Hospital setting				<.001
Urban	2575 (98.2)	389 (94.0)	2186 (99.0)	
Rural	48 (1.8)	25 (6.0)	23 (1.0)	
Hospital size, No. of beds				<.001
0–199	59 (2.3)	26 (6.3)	33 (1.5)	
200–399	290 (11.1)	67 (16.2)	223 (10.1)	
≥400	2274 (86.7)	321 (77.5)	1953 (88.4)	
Teaching hospital	2412 (92.0)	350 (84.5)	5960 (93.4)	<.001
Attending physician type (n = 2552)				<.001
Hospitalist or primary care provider	1053 (41.3)	222 (55.2)	831 (38.7)	
Hematology/oncology	960 (37.6)	105 (26.1)	855 (39.8)	
Pulmonary/critical care	257 (10.1)	35 (8.7)	222 (10.3)	
Surgery	142 (5.6)	21 (5.2)	121 (5.6)	
Other	140 (5.5)	19 (4.7)	121 (5.6)	
Outcomes				
Length of hospitalization, d, median (IQR)	15.0 (7–29)	21.0 (11–35)	14.0 (7–28)	<.001
ICU admission	1376 (52.5)	254 (61.4)	1122 (50.8)	<.001
In-hospital death	327 (12.3)	78 (18.8)	249 (11.3)	<.001
Underlying conditions, complications, and symptoms				
Asthma	162 (6.2)	21 (5.1)	141 (6.4)	.309
Autoimmune/inflammatory disease	178 (6.8)	30 (7.3)	148 (6.7)	.685
COPD	422 (16.1)	89 (21.5)	333 (15.1)	.001
COVID-19 (n = 1945)[b]	260 (13.4)	57 (18.7)	203 (12.4)	.003
Cystic fibrosis	59 (2.3)	[a]	[a]	.232
Diabetes	849 (32.4)	131 (31.6)	718 (32.5)	.731
Diarrhea	377 (14.4)	68 (16.4)	309 (14.0)	.195
Fungal disease	860 (32.8)	243 (58.7)	617 (27.9)	<.001
Gastrostomy	47 (1.8)	11 (2.7)	36 (1.6)	.148
Hematologic malignancy	1242 (47.4)	138 (33.3)	1104 (50.0)	<.001
HIV	60 (2.3)	20 (4.8)	40 (1.8)	<.001
Immunosuppressive disorder besides HIV	490 (18.9)	70 (16.9)	420 (19.0)	.313
Influenza	35 (1.3)	[a]	[a]	.807
Liver disease	278 (10.6)	51 (12.3)	227 (10.3)	.215
Mucositis	266 (10.4)	39 (9.4)	227 (10.3)	.597
Neutropenia	679 (25.9)	96 (23.2)	583 (26.3)	.172

Table 1. Continued

Characteristic	Total (N = 2623)	TDM Performed (n = 414)	TDM Not Performed (n = 2209)	*P* Value
Obesity	397 (15.1)	77 (18.6)	320 (14.5)	.032
Pneumonia	946 (36.1)	203 (49.0)	743 (33.6)	<.001
Sepsis	759 (28.9)	147 (35.5)	612 (27.7)	.001
Solid organ malignancy	158 (6.0)	36 (8.7)	122 (5.5)	.013
Transplant and complications	368 (14.0)	53 (12.8)	315 (14.3)	.433
Tuberculosis	[a]	[a]	[a]	.018
Vomiting	11 (0.4)	[a]	[a]	.007

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; TDM, therapeutic drug monitoring.

[a]Number suppressed due to cell size <10 or cell that would enable calculation of <10 hospitalizations.

[b]Among 2020–2021 hospitalizations only.

(66.9%) had 1 TDM test, 98 (23.7%) had 2 TDM tests, and 39 (9.4%) had ≥3 tests.

The median first TDM result (μg/mL) was 1.2 (range, 0.2–5.5) for itraconazole plus hydroxyitraconazole, 1.45 (range, 0.3–5.6) for posaconazole, and 2.4 (0.1–17.3) for voriconazole (Supplementary Table 2). Among 47 hospitalizations with itraconazole plus hydroxyitraconazole TDM, the first result was <1.0 μg/mL in 36.2%. Among 296 hospitalizations with voriconazole TDM, 20.9% had a first result <1.0 μg/mL and 16.2% had a first result of >5.5 μg/mL. Among 50 hospitalizations with posaconazole TDM, 28.0% had a first result of ≤1 μg/mL. Fewer than 10 hospitalizations each had first posaconazole results ≤0.7 μg/mL or >4 μg/mL.

Compared with TDM-eligible hospitalizations in which TDM was not performed, TDM was more frequent among hospitalizations involving longer hospital stays (median, 21.0 vs 14.0 days; $P < .001$), intensive care unit stays (61.4 vs 50.8%; $P < .001$), and in-hospital death (18.8% vs 11.3%; $P < .001$). TDM was also more frequent among hospitalizations with pneumonia (49.0% vs 33.6%; $P < .001$), sepsis (35.5% vs 27.7%; $P = .001$), fungal disease (58.7% vs 27.9%; $P < .001$), and obesity (18.6% vs 14.5%; $P = .032$) but less frequent among those with hematologic malignancy (33.3% vs 50.0%; $P < .001$). Among the 860 TDM-eligible hospitalizations with a fungal disease, aspergillosis was the most common type (n = 370 [43.0%]) (Supplementary Table 3). By drug, the percentage of hospitalizations with a fungal disease was 61.4% for itraconazole, 18.9% for posaconazole, and 37.1% for voriconazole.

Regardless of TDM data availability in PHD, 34 479 total TDM-eligible hospitalizations occurred among 720 hospitals. The 31 856 TDM-eligible hospitalizations excluded from the main analysis due to lack of TDM data were more likely to involve older, female, and Hispanic patients and those from rural, smaller or midsize, nonteaching hospitals and the West region compared with those with TDM data available (Supplementary Table 4).

DISCUSSION

In this hospital-based administrative and laboratory dataset, TDM was uncommonly performed (~16%) among a large cohort of patients for whom TDM is recommended, signifying missed opportunities to monitor antifungal drug levels and potentially improve clinical outcomes. The TDM use rate in this analysis was lower than a previous study's overall TDM use rate of 41% among patients receiving isavuconazole, posaconazole, or voriconazole for treatment or prophylaxis of invasive fungal infections at 55 (predominately academic) medical centers [5]. Differences in study design and facility-level characteristics might explain these differences in TDM use. Our analysis further suggests that TDM might be unavailable at many facilities given the small number of hospitals (n = 50) contributing TDM data to PHD. Future studies are needed to better understand and address barriers to TDM use, which might also include high costs and uncertainty around TDM guidelines and interpretation of results [7].

TDM was more common among hospitalizations involving a fungal disease diagnosis than those without, suggesting that clinicians might be more familiar with using TDM during treatment than during antifungal prophylaxis. Rates of TDM were particularly low (5.7%) for posaconazole-associated hospitalizations, most of which likely involved posaconazole prophylaxis given the low rate of fungal disease diagnosis and higher rate of associated hematologic malignancy; this might reflect controversy surrounding whether TDM is beneficial for all patients receiving posaconazole, particularly those receiving prophylaxis [8].

Compared with posaconazole and voriconazole, the higher TDM use among patients receiving itraconazole is not surprising given its well-established unpredictable oral bioavailability and known drug interactions. Certain factors (eg, longer hospitalization length, higher mortality, pneumonia, sepsis) suggested that TDM was used more frequently in patients with severe illness, consistent with existing guidance. The higher observed use of TDM in patients with obesity, who may require dose

adjustments, was also consistent with guidance. We did not find significantly greater TDM use among pediatric patients, who may have variations in volume of distribution and clearance compared with adults; patients with liver disease, which impairs clearance of antifungals; and patients with diagnosis codes for "diarrhea (unspecified)," which might indicate issues with drug absorption and volume of distribution [2]. Overall, our analysis suggests opportunities for increased TDM use among all hospitalized patients receiving itraconazole, posaconazole, or voriconazole for certain patient populations.

Target therapeutic ranges for these azoles are not firmly established and may vary by institution, disease, or disease severity. Ideal concentrations are generally accepted as 1 μg/mL for prophylaxis and ≥2 μg/mL for treatment for itraconazole plus hydroxyitraconazole levels, ≥0.7 μg/mL for prophylaxis and >1.0 μg/mL for treatment with posaconazole, and 1–5.5 μg/mL for voriconazole [1, 2, 9]. The upper threshold for itraconazole is approximately 3 μg/mL but can vary based on analytic methods [2]. Although an upper limit for posaconazole is not well-established, posaconazole-induced pseudohyperaldosteronism might be more likely as trough levels exceed 3 μg/mL [10].

Our results showed that nearly one-quarter of first TDM results were potentially subtherapeutic, and 16% of first results for voriconazole were high enough to potentially cause central nervous system symptoms, hepatoxicity, or other adverse events, similar to another study which found that 31% of TDM results were outside the therapeutic range [11]. As antifungal resistance continues to emerge, achieving adequate serum drug concentrations is critical to prevent resistance from treatment pressure [4]. Furthermore, nearly one-third of hospitalizations in which itraconazole TDM was performed did not have concurrent hydroxyitraconazole testing. Hydroxyitraconazole metabolite has antifungal activity and potency similar to itraconazole and may not be accounted for by measuring itraconazole levels alone, but further research to determine the clinical significance of hydroxyitraconazole levels is needed as robust evidence for this practice does not exist. Currently, therapeutic trough targets are based on itraconazole alone measured by chromatographic assays.

Study limitations include the possibility of incorrectly excluding hospitalizations from hospitals where TDM was available but not performed, leading to an overestimate of TDM use. Representativeness and generalizability might also be an issue; the facility-level characteristics (eg, rural, smaller, nonteaching status) associated with TDM use we observed might be due to the patient population served at those facility types, which likely includes fewer patients with hematologic malignancies than at large academic medical centers. Further limitations include potential misrepresentation of underlying conditions and complications using *ICD-10* codes, the inability to capture prehospitalization antifungal use and TDM use, and lack of information about antifungal indication. Last, we did not examine the role of TDM in patient outcomes or evaluate TDM use for isavuconazole, fluconazole, or echinocandins, which would be useful for further study [12].

Given the low observed TDM use among hospitalized patients taking itraconazole, posaconazole, or voriconazole, future work is needed to increase and optimize TDM and identify and address barriers to its use.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank James Baggs and Bailey Wallace for assistance with data analysis preparation.

Ethics statement. This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy (eg, 45 Code of Federal Regulations [C.F.R.] part 46.102(l)(2), 21 C.F.R. part 56; 42 United States Code [U.S.C.] §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq). This study did not include factors necessitating patient consent. PINC-A1 Healthcare Database data are fully de-identified, so this analysis was not subject to review by the CDC institutional review board.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Potential conflicts of interest. All authors: No reported conflicts.

References

1. Patterson TF, Thompson GR III, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 63:e1–60.
2. John J, Loo A, Mazur S, Walsh TJ. Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients. Expert Opin Drug Metab Toxicol **2019**; 15:881–95.
3. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother **2014**; 69: 1162–76.
4. Fisher MC, Alastruey-Izquierdo A, Berman J, et al. Tackling the emerging threat of antifungal resistance to human health. Nat Rev Microbiol **2022**; 20:557–71.
5. Ostrosky-Zeichner L, Nguyen MH, Bubalo J, et al. Multicenter registry of patients receiving systemic mold-active triazoles for the management of invasive fungal infections. Infect Dis Ther **2022**; 11:1609–29.
6. PINC AI Applied Sciences. PINC AI healthcare data—special release: COVID-19. **2021**. Available at: https://offers.premierinc.com/rs/381-NBB-525/images/PHD_COVID-19_White_Paper.pdf. Accessed 12 January 2023
7. Ates HC, Roberts JA, Lipman J, Cass AEG, Urban GA, Dincer C. On-site therapeutic drug monitoring. Trends Biotechnol **2020**; 38:1262–77.
8. Cornely OA, Ullmann AJ. Lack of evidence for exposure-response relationship in the use of posaconazole as prophylaxis against invasive fungal infections. Clin Pharmacol Ther **2011**; 89:351–2.
9. Wiederhold NP, Schwartz IS, Patterson TF, Thompson GR III. Variability of hydroxy-itraconazole in relation to itraconazole bloodstream concentrations. Antimicrob Agents Chemother **2021**; 65:e02353-20.
10. Nguyen MH, Davis MR, Wittenberg R, et al. Posaconazole serum drug levels associated with pseudohyperaldosteronism. Clin Infect Dis **2020**; 70:2593–8.
11. McCreary EK, Bayless M, Van AP, et al. Impact of triazole therapeutic drug monitoring availability and timing. Antimicrob Agents Chemother **2019**; 63: e01245-19.
12. Gómez-López A. Antifungal therapeutic drug monitoring: focus on drugs without a clear recommendation. Clin Microbiol Infect **2020**; 26:1481–7.