

Factors Influencing Posaconazole Concentrations in Hospitalized Patients Receiving Delayed Release Tablets

Vini J. Vyas¹, Krizten Ortiz¹, Mohanad Al Obaidi, MD, MPH, FIDSA², David E. Nix, PharmD, BCPS, BCIDP^{1,3}

¹University of Arizona R. Ken Coit College of Pharmacy, ²Banner University Medical Center Tucson, ³University of Arizona College of Medicine



Pharmacy



THE UNIVERSITY OF ARIZONA
R. Ken Coit
College of Pharmacy



Banner
University Medical Center



THE UNIVERSITY OF ARIZONA
College of Medicine
Tucson

INTRODUCTION

Background

- Triazole antifungal agents are frequently used for the prevention and treatment of invasive fungal infections (IFIs). Their clinical utilization remains complicated due to extensive drug-drug interactions and highly variable pharmacokinetic profiles. The Society of Infectious Disease Pharmacists recommends therapeutic drug monitoring (TDM) for triazoles employed in the prophylaxis and treatment of IFIs.⁶
- Globally, an estimated 1.9 million people are diagnosed with an acute form of IFI every year and an estimated 3 million are diagnosed with a chronic form of IFI every year.³ According to the CDC, the crude mortality rate for patients with candidemia in hospitalized patients exceeds 25%, and the one-year survival for invasive aspergillosis is 59% among solid organ transplant recipients and 25% among stem cell transplant recipients.¹
- Banner University Medical Center Tucson and Phoenix campuses (BUMCT/BUMCP) in Arizona experience a range of patients who require care for invasive fungal infections. Current BUMCT/BUMCP practices include the use of posaconazole delayed release tablets (DRT) in the prophylaxis and treatment of IFIs.
- Target serum posaconazole concentrations of ≥ 0.7 mg/L for prophylaxis and ≥ 1 mg/L for treatment are recommended for the IFIs.² Despite the Society of Infectious Disease Pharmacists recommendation for the use of TDM in mold-active triazoles⁶, significant variations in drug concentrations continue to be seen among patients treated with posaconazole.

Aim

- This retrospective study sought to determine the percentage of patients who achieved a therapeutic drug serum concentration and investigated influencing factors involved in suboptimal serum concentrations among patients treated with posaconazole DRT at BUMCT/BUMCP. Electronic medical records were utilized from BUMCT and BUMCP.

METHODS

Data Collection

Inclusion:

- Obtained list of patients with > 1 measured serum posaconazole concentration
- Dosing administration records were extracted
- Analyzable events required a serum posaconazole concentration with at least 5 days of documented preceding doses with datetimes

Exclusion:

- Outpatient serum concentrations without documented preceding doses
- Patients who received doses in the hospital but had serum levels drawn after discharge in outpatient setting
- Some patients had multiple TDM events however, initial analysis focused on the first event

Factors explored as covariates included:

- Age, sex, weight, BMI, solid organ transplant, cancer, solid tumor, hematologic cancer, severe neutropenia, history of GI disease/surgery, posaconazole DRT crushing, diet, feeding tube usage, nutritional supplementation, presence of diarrhea or mucositis, chronic kidney disease stage, liver function, and concomitant medications (statins, metabolic inducers, acid suppressors, metoclopramide, antacids, sucralfate, corticosteroids)

Measures:

- Structure: Number of hospitalized patients ≥ 18 years of age with at least one serum posaconazole concentration who received at least 5 days of treatment with posaconazole DRT
- Explored factors potentially influencing aSPC
- Correction of hypoalbuminemia resulting in adjusted SPC (ASPC = $SPC * 1 / (0.01 + 0.99 * ALB/4.4)$)
- Outcome: Number of patients who achieved targeted serum posaconazole concentrations

Statistical Analysis

- Data was analyzed using Fisher's exact test using SAS version 9.4 (SAS Institute, Cary, NC)

RESULTS

Table 1. Baseline patient demographics

N = 40	
Gender (Male)	30 (75%)
Mean Age (Years)	60.5 \pm 12.0
BMI	27.5 \pm 6.14
SOT (Lung, Heart, Kidney, Liver)	27 (18, 2, 4, and 3)
Cancer (Solid Tumors, Leukemia/Lymphoma)	10 (7, 3)

Figure 1. Reported Posaconazole Trough

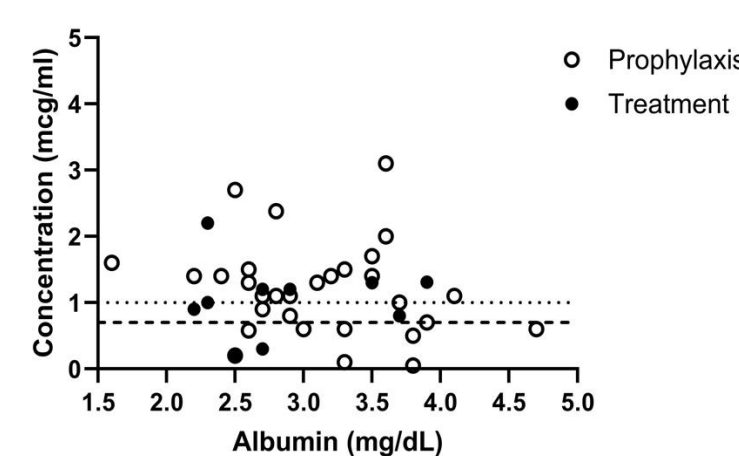


Figure 2. Adjusted Posaconazole Trough

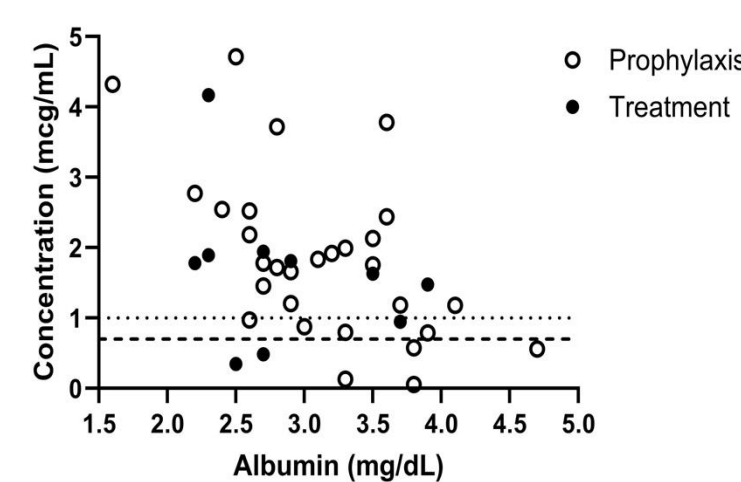


Figure 3. Reported-Adjusted Concentration

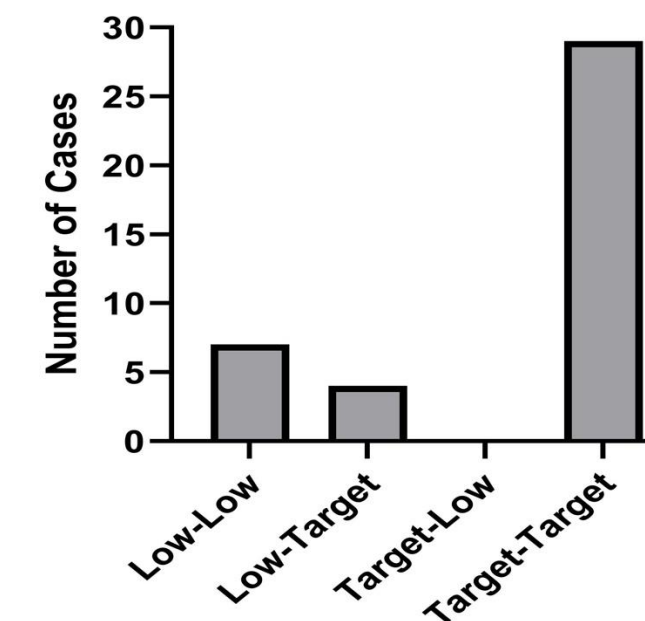


Figure 3. Concentrations reported as 'low' (27.5%) resulted in a categorical change from 'low' to 'target' in 10% of cases ($p < 0.001$) after albumin adjustment. Concentrations reported as 'target' showed no categorical change after albumin adjustment.

- Acid suppression with pantoprazole ($n=23$) or famotidine ($n=8$) was not associated with low aSPC ($p=0.175$)
- No association was found between antacid administration and low aSPC; aluminum-based antacid was used in ($n=13$) and calcium carbonate ($n=3$) with $p=1$. Only one patient received sucralfate
- No association was observed between metoclopramide administration and changes in SPC; it was used in 1 of 6 patients with low SPC, compared to 3 of 32 with target aSPC ($p=0.513$)
- Only 1 patient received a metabolic-inducing agent (rifabutin), and both had target aSPC
- Prednisone was received by 19 patients, and 9 received other corticosteroids; 4 of 7 patients had a low aSPC and 24 of 33 patients had a target aSPC ($p=0.410$)
- Only 1 patient received a crushed tablet formulation, and this patient had a low aSPC (0.6 mg/L)
- 2 patients had mucositis, and both had target aSPC
- 5 patients had diarrhea, with 2 of these (40%) having low aSPC, compared to 5 of 35 (14.3%) had low aSPC without diarrhea ($p=0.209$)
- No evidence of an association between chronic kidney disease and low aSPC
- Only 1 patient had alkaline phosphatase of 1540 U/L and bilirubin of 30.5 mg/dL, along with low aSPC. Overall, no associated was found between elevated liver function tests and aSPC

DISCUSSION

Implications

- Adjusted serum posaconazole concentrations resulted in more patients being therapeutic

Limitations

- Lack of consistent chart documentation (e.g., diet/supplementation, presence of diarrhea or mucositis)
- Non-adherence to TDM monitoring protocol (e.g., concentrations collected too early/drawn late)
- Lack of generalizability of the study findings to other populations (data was solely collected from BUMCT/BUMCP)
- Small sample size
- Majority of concentrations were drawn outside the hospital setting therefore adherence to posaconazole was not accessible

Need for Further Study

- Distinguish reasons for low aSPC, capturing bioavailability, and potentially rapid posaconazole clearance
- Investigate genetic determinants of low bioavailability and rapid drug clearance
- Investigate treatment outcome related to SPC/aSPC (Pharmacodynamic theory supports use of aSPC)⁷

CONCLUSION

- Given that free concentrations determine antifungal activity and drug disposition, use of aSPC in cases of hypoalbuminemia is recommended
- We were unable to identify the factors responsible for low aSPC
- More detailed PK monitoring is needed to differentiate between poor bioavailability versus rapid elimination is needed

REFERENCES

- Centers for Disease Control and Prevention. (n.d.). Data and statistics on aspergillosis. Centers for Disease Control and Prevention. <https://www.cdc.gov/aspergillosis/statistics/index.html>
- Chin, A., Pergam, S. A., Fredricks, D. N., Hoofnagle, A. N., Baker, K. K., & Jain, R. (2017). Evaluation of Posaconazole Serum Concentrations from Delayed-Release Tablets in Patients at High Risk for Fungal Infections. *Antimicrobial agents and chemotherapy*, 61(10), e00569-17. <https://doi.org/10.1128/AAC.00569-17>
- Dieringer, T. D., Schaeferman, J. M., & Davis, M. R. (2022). Enteral feeding tube administration with therapeutic drug monitoring of crushed posaconazole tablets and opened isavuconazonium sulfate capsules. *The Journal of antimicrobial chemotherapy*, 77(5), 1417-1423. <https://doi.org/10.1093/jac/dkac035>
- Dolton, M. J., Ray, J. E., Chen, S. C., Ng, K., Pont, L., & McLachlan, A. J. (2012). Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. *Antimicrobial agents and chemotherapy*, 56(11), 5503-5510. <https://doi.org/10.1128/AAC.00802-12>
- Fang, W., Wu, J., Cheng, M., Zhu, X., Du, M., Chen, C., Liao, W., Zhi, K., & Pan, W. (2023). Diagnosis of invasive fungal infections: challenges and recent developments. *Journal of biomedical science*, 30(1), 42. <https://doi.org/10.1186/s12929-023-00926-2>
- McCreary, E. K., Davis, M. R., Narayanan, N., Andes, D. R., Cattaneo, D., Christian, R., Lewis, R. E., Watt, K. M., Wiederhold, N. P., & Johnson, M. D. (2023). Utility of triazole antifungal therapeutic drug monitoring: Insights from the Society of Infectious Diseases Pharmacists: Endorsed by the Mycoses Study Group Education and Research Consortium. *Pharmacotherapy*, 43(10), 1043-1050. <https://doi.org/10.1093/ptp/ptad035>
- Nix DE, Al-Obaidi M, Zangeneh T. Hypoalbuminemia and Posaconazole Therapeutic Drug Monitoring. *Open Forum Infect Dis*. 2024 Aug 9;11(8):ofae452. doi: 10.1093/ofid/ofae452. PMID: 39205926; PMCID: PMC11350285.
- Patterson, T. F., Thompson, G. R., 3rd, Denning, D. W., Fishman, J. A., Hadley, S., Herbrecht, R., Kontoyiannis, D. P., Marr, K. A., Morrison, V. A., Nguyen, M. H., Segal, B. H., Steinbach, W. J., Stevens, D. A., Walsh, T. J., Wingard, J. R., Young, J. A., & Bennett, J. E. (2016). Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 63(4), e1-e60. <https://doi.org/10.1093/cid/ciw326>
- Yi, W. M., Schoeppler, K. E., Jaeger, J., Mueller, S. W., MacLaren, R., Fish, D. N., & Kiser, T. H. (2017). Voriconazole and posaconazole therapeutic drug monitoring: a retrospective study. *Annals of clinical microbiology and antimicrobials*, 16(1), 60. <https://doi.org/10.1186/s12941-017-0235-8>