International Journal of Basic & Clinical Pharmacology
Nandan A et al. Int J Basic Clin Pharmacol. 2025 Nov;14(6):931-936
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20253365

Original Research Article

Echoes of adversity with Voriconazole: a retrospective study

Akhila Nandan*, Princy Louis Palatty, Laxmi Govindraj

Department of Pharmacology, Amrita Institute of Medical sciences, Amrita Viswa Vidhyapeedham, Kochi, India

Received: 22 September 2025
Revised: 13 October 2025
Accepted: 14 October 2025

***Correspondence:**
Dr. Akhila Nandan,
Email: akhilasyama331@gmail.com

ABSTRACT

Background: Voriconazole is widely used in managing invasive fungal diseases, but its adverse drug reactions, pose significant clinical challenges. This retrospective observational study aimed to evaluate the frequency, severity, and risk factors of ADRs associated with voriconazole treatment in patients in a tertiary care hospital, focusing on demographic characteristics, co-morbidities, route of administration, and trough drug levels.

Methods: Data of 95 patients who received voriconazole between 2020 and 2025 were retrieved from electronic medical record. Demographic details, treatment indication, comorbidities, mode of administration, and trough plasma concentrations were collected. ADRs were categorized by system organ class, assessed for severity using modified Hartwig -Siegel scale, and causality was determined using the WHO-UMC system. Statistical analysis employed chi-square tests for categorical variables and Mann–Whitney U tests for trough level comparisons, with $p<0.05$ considered significant.

Results: ADRs occurred in 58 patients (61.1%), hepatobiliary were most frequent (44%). Male patients had a higher ADR rate (54.5%), and those with type 2 diabetes mellitus showed a significantly higher incidence ($p=0.008$). Cardiovascular comorbidities and thyroid disorders were also significantly associated with ADRs. The intravenous route showed a higher incidence of ADRs compared to oral route. Most reactions were moderately severe (56.8%). A statistically significant relationship was observed between higher trough concentrations and the occurrence of transaminitis.

Conclusion: Voriconazole therapy showed a high rate of moderate ADRs, primarily hepatobiliary. Intravenous route and comorbidities-diabetes, cardiovascular disease, and thyroid disorders-were significant risk factors requiring vigilant monitoring.

Keywords: Voriconazole, Adverse drug reactions, Hepatotoxicity, Therapeutic drug monitoring, Diabetes mellitus

INTRODUCTION

Voriconazole is a second-generation triazole antifungal drug commonly employed for invasive fungal infections like aspergillosis and fluconazole resistant Candida infections.[1] While initial clinical trials indicated liver enzyme elevation in about 11–19 percent of patients and treatment discontinuation in up to 20 percent, real-world observational experience documented hepatotoxicity rates as high as 60–69 percent in high risk patients.[1-3] Hepatotoxicity invariably ranks as the most frequent and clinically significant adverse drug reaction (ADR) with voriconazole.[2] Pharmacokinetic studies and meta-analyses have proposed that trough plasma levels >5.5 mcg/ml enhance the risk of hepatotoxicity, although thresholds are variable. A therapeutic range of ~1.0–5.5µg/ml is widely accepted to balance efficacy and safety.[2,4] Interestingly, genetic polymorphisms in CYP2C19 significantly influence voriconazole metabolism, leading to large interpatient variability in drug exposure.[5] Although CYP2C19 genotype–phenotype associations impact plasma levels, existing data does not consistently predict occurrence of hepatotoxic ADRs.[2,5] Case series and pharmacovigilance reports have also characterized

neurological ADRs like hallucinations and visual disturbances, often in the context of higher trough levels (> 5 µg/ml).[6] Comorbid conditions like type 2 diabetes mellitus and cardiovascular comorbidities have not been investigated comprehensively as independent risk factors for voriconazole-associated ADRs. This retrospective study was performed to evaluate the frequency, severity, and causality of ADRs related to voriconazole in adult patients and to analyze possible risk factors such as administration route (intravenous vs. oral), sex, and other comorbidities.

METHODS

A retrospective observational study was conducted at the Amrita Institute of Medical Sciences, Kochi, India. Inclusion criteria were all patients who underwent voriconazole treatment within five years (2020-2025). The n=95 was the predefined sample size that was identified from available medical records. Patient age, sex, co-morbidities, method of administration of voriconazole (oral vs intravenous), and trough plasma concentration as recorded in the clinical record were pre-specified variables for data collection identified from electronic medical records. The inclusion criteria were all patients who received Voriconazole. The exclusion criteria were people with poor general condition, already existing end stage renal disease, patients already having hepatic dysfunction (grade 3 fatty liver and above). Drug adverse effects (ADRs) were assessed by following methods i.e., First, a list of organ systems most commonly affected by drug side effects (e.g., hepato-biliary; neurological) was prepared, then Severity is graded based on Modified Hartwig & Siegel severity scale and finally Causality was determined as per WHO-UMC system.[8]

Categorical data was expressed as proportions and the statistical plan developed a priori, before the data were examined specified that chi-square tests would be used to compare categorical contrasts (e.g., the proportion of ADR by sex or diabetes status); Mann-Whitney U tests would be utilized when continuous variables (e.g., trough concentrations by administration route) were compared. The level of significance was $p<0.05$. Ethical clearance from the Institutional Ethics Committee (IEC approval number: ECASM-AIMS-2025-231) was obtained. A waiver of informed consent was permitted since the data collection was retrospective and anonymized. The study protocol furthermore strictly adhered to the ethical principles.

RESULTS

In the course of the study, 95 patients underwent voriconazole therapy. Sixty-two of these latter were female and 33 males, and the median age was 61 years (IQR 47-69) The most frequent reasons for the administration of voriconazole among our patients included fungal pneumonia (34.7%), osteomyelitis of skull (9.5%), invasive aspergillosis (8.4%), aspiration pneumonia (7.3%) and sepsis (7.3%), other indications were 5.2%The dosing was Q12H. The most frequent underlying comorbidities identified were type 2 diabetes mellitus (n=47, 49.5%) and hypertension (n=42, 44.2%) (Table 1). At least one adverse drug reaction (ADRs) was found in 58 (61.1%) of the patients. The most frequently occurring ADRs were transaminitis (44.2%), followed by disorientation (27.4%). Visual disturbances were rare (1.1%), and cutaneous and other systemic ADRs were not seen.

The majority of the ADRs were of moderate (56.8%) or mild (38.9%) grade according to the Modified Hartwig and Siegel Severity Scale, while only 3 patients (3.2%) had severe reactions. Serious adverse events were seen in 12 patients (%) who required prolongation of hospital stay and intensive medical care for the ADR (Table 2).

Based on the WHO-UMC criteria, most hepatobiliary and neurological ADRs were "possible" or "probable" by causality assessment. Voriconazole therapy was discontinued in 49.5% of patients who experienced ADRs (Figure 1).

Table 1: Demographic and clinical profiles of the patients.

Characteristics	Patients (n=95) (%)
Sex	
Women	62 (65.3)
Men	33 (34.7)
Age (in years)	
Median (range)	57 (5–91)
Mean (SD)	56.08 (18.97)
Voriconazole indication	
Fungal pneumonia	33 (34.7)
Invasive aspergillosis	8 (8.4)
Skull base osteomyelitis	9 (9.5)
Aspiration pneumonia	7 (7.3)
Bronchiectasis	4 (4.2)
Sepsis	7 (7.3)
Fungal ball	6 (6.3)

Continued.

Characteristics	Patients (n=95) (%)
Parapneumonic effusion	5 (5.2)
Pyrexia of unknown origin	3 (3.2)
Eye infection	2 (2.1)
Eye infection	2 (2.1)
Non respiratory infection	4 (4.2)
Other indications	5 (5.2)
Underlying medical conditions	
Type 2 Diabetes mellitus	47 (49.5)
Hypertension	42 (44.2)
Coronary artery disease	15 (15.8)
Chronic kidney disease	6 (6.3)
Malignancy	7 (7.4)
Chronic liver disease	2 (2.1)
Cerebrovascular accident	6 (6.3)
Thyroid disorders	10 (10.5)
Voriconazole route of administration	
Oral	50 (52.6)
Intravenous	44 (46.3)
Other	1 (1.1)
Concomitant medications	
Antihypertensives	35 (36.8)
Antidiabetics	43 (45.3)
Antiplatelets	15 (15.8)
Anticoagulants	1 (1.1)
Prior Antibiotics/Antifungals	6 (6.3)

Table 2: Details of reported adverse drug reactions (ADRs).

ADRs	Reports (%)	Serious (%)	Causality (WHO-UMC) (%)	Outcome (%)
Total	58 (61.1)	4 (6.9)	Possible: 44 (75.8), Probable: 14 (24.1)	
Transminitis	42 (44.2)	4 (9.5%)	Possible: 34 (81.0), Probable: 8 (1.9)	Drug stopped: 32 (76.2)
Disorientation	26 (27.4)	4 (15.4%)	Possible: 25 (96.1), Probable: 1 (3.8)	Drug stopped: 25 (96.2)
Visual disturbances	1 (1.1)	0 (0%)	Possible: 1 (100), Probable: 0 (0)	Drug stopped:1 (100)

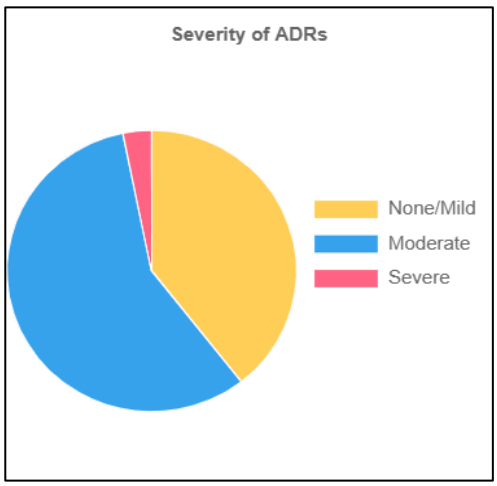

Figure 1: Severity of ADRs by Modified Hartwig and Siegel scale.

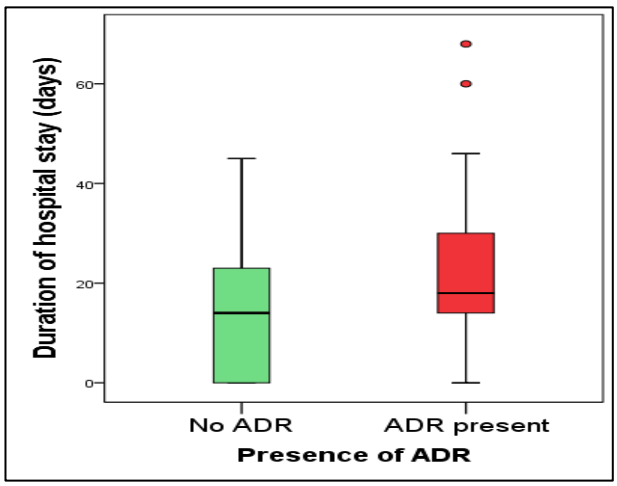

Figure 2: Box plot comparing occurrence of ADR and length of hospital stay.

Trough levels were examined in 12 patients. Of these, 7 patients had voriconazole levels ≤5.5 mg/l and 5 had levels >5.5 mg/l. Transminitis was seen in all patients with high trough level (Table 3). ADRs occurred more often in diabetic patients (p=0.008), hypertensives (p=0.002), CAD (p=0.027), CVA (p=0.043) and thyroid disorders (p=0.02) No statistically significant correlation with ADRs was shown for age, gender, CKD, CLD, malignancy. Frequency of ADRs was more with IV route compared to oral route (Table 4).

Table 3: Association of patient factors with occurrence of ADRs (n=95).

Factor	Group	Total patients	Patients with ADR	ADR (%)	P value (Chi-Square)
Age group (in years)	Paediatric (<18)	6	5	83.3	0.614
	Young Adult (18–39)	10	6	60	
	Middle-aged (40–64)	39	23	59	
	Elderly (65+)	40	24	60	
Gender	Men	33	18	54.5	0.297
	Women	62	40	64.5	
T2DM	Yes	47	35	74.4	0.008*
	No	48	24	50	
Hypertension	Yes	42	33	78.5	0.002*
	No	53	29	54.7	
CAD	Yes	15	13	86.7	0.027*
	No	80	48	60	
CKD	Yes	6	4	66.7	0.749
	No	89	54	60.7	
Malignancy	Yes	7	4	57.1	0.796
	No	88	54	61.4	
CLD	Yes	2	1	50.0	0.686
	No	93	57	61.3	
CVA	Yes	6	6	100	0.043*
	No	89	53	59.6	
Thyroid disorders	Yes	10	10	100	0.028*
	No	85	51	60	
Route of administration	Oral	50	22	65.9	0.02*
	Intravenous	44	35	58	
	Other	1	1	0	

*chi-square test was used as test of significance, p<0.05 was considered statistically significant

Table 4: Shows the correlation between voriconazole trough levels and drug induced liver injury.

ADRs	Voriconazole level ≤5.5 mg/l (n=7)	Voriconazole level ≥5.5 mg/l (n=5)	P value
Hepatobiliary	0	5 (100%)	0.001*

*-Significant.

Table 5: Comparison of voriconazole trough levels by route of administration is provided.

Route of administration	No. of patients (n=11)	Mean trough level (mg/l)	SD (mg/l)	P value (Mann-Whitney U)
Oral	6	4	2.24	0.268
Intravenous	5	6	2.74	

Comparison of voriconazole trough levels by route of administration was found to be higher among intravenous therapy patients as compared to oral therapy patients though this difference was not found to be statistically significant (Table 5). The (Figure 2) also shows that the duration of the hospital stay was more in patients with ADR than without ADR (p=0.011)

DISCUSSION

This research identified a high prevalence (61.1%) of adverse drug reactions (ADRs) among patients treated with voriconazole, with hepatotoxicity and disorientation being the two most prevalent. The majority of ADRs were of moderate intensity, and almost half necessitated stopping

the drug. Interestingly, type 2 diabetes mellitus (T2DM), hypertension, coronary artery disease, cerebrovascular disease, thyroid disorder, IV route of administration were identified as having an association with incidence of ADRs. The incidence of ADR has also increased the duration of hospital stay, affecting the patient related outcome. These results validate the necessity for individualized monitoring beyond plasma concentration criteria alone.

Few of the earlier studies have addressed voriconazole toxicity, but few have analyzed in a systematic fashion the combined impact of route of administration, plasma levels, and host comorbidities. A recent meta-analysis intimated that plasma trough concentrations >5.5 mg/l could anticipate hepatotoxicity.[2,4] In the study, voriconazole-induced hepatotoxicity was predominantly manifested as transaminitis, in contrast to earlier reports where cholestatic or mixed patterns were more frequent. For example, a large Chinese cohort found nearly equal proportions of hepatocellular (5.01%) and cholestatic (5.19%) injury, case reports have also described predominantly cholestatic presentations, such as a patient with fungal pneumonia developing marked ALP and GGT elevations after voriconazole therapy.

Furthermore, pharmacogenetic studies demonstrate that CYP2C19 poor and intermediate metabolizers have higher voriconazole trough concentrations and increased risk of hepatotoxicity. The predominance of transaminitis in our cohort may be attributed to host factors such as CYP2C19 polymorphisms leading to higher drug exposure, concomitant medications, or metabolic risk factors predisposing to hepatocellular injury, as well as differences in monitoring and diagnostic criteria across studies. and in our study also, despite limited sample size of measured trough levels, all patients with elevated trough had hepatotoxicity (transaminitis). This correlation in this cohort also supports the increasing awareness of therapeutic drug monitoring (TDM), while being crucial, not being the only factor determining safety of treatment.

The novel association of T2DM, cardiovascular comorbidities and thyroid disorders and enhanced ADR risk provide an arena to explore in more detail. The increased incidence of ADR in diabetics could be due to variation in pharmacokinetic and pharmacodynamics of drugs. Slow gastric emptying, slower absorption, decrease in plasma protein binding due to non-enzymatic glycation of albumin, decreased tissue penetration due to reduced vascular permeability and microvascular changes, all could explain why Voriconazole induced ADRs is more seen in diabetics.[14] Baseline hepatic susceptibility, oxidative stress, and hyperglycemia in diabetic patients can contribute to increased drug-induced liver injury susceptibility. This observation should be explored further, especially considering that diabetes is common among populations at risk for invasive fungal infections. Also, the finding of increased frequency of ADR with cardiovascular comorbidities and thyroid disorders has not been found in any prior studies. A plausible explanation is that many comorbidities affect liver and kidney function, even sub clinically. For example, HTN and CAD can lead to chronic vascular changes reducing hepatic perfusion. CVA may be associated with impaired autonomic or renal function. Thyroid disorders affect CYP activity, as hypo or hyperthyroidism alters metabolism of voriconazole. Poor metabolic control can increase drug exposure and ADR risk.

Contrary to reports implicating female sex as risk factor, slightly elevated ADR rates in males were found (54.5%), which agrees with recent trends in pharmacovigilance.[13] This further stresses the requirement of sex-specific pharmacokinetic and pharmacodynamic studies. These results add evidence to the trend towards combined monitoring approaches that harmonize clinical risk factors with pharmacokinetics instead of relying on trough levels alone. For diabetic patients and patients with cardiovascular comorbidities and thyroid disorders specifically, more intensive monitoring and potential dose modification may be indicated. Ongoing research would seek to identify mechanisms by which diabetes and cardiovascular comorbidities along with thyroid disorders include pharmacogenomic stratification, and confirm these results with prospective multicentre cohorts. Ultimately, these findings add to a body of evidence supporting the use of individually tailored voriconazole therapy based on broad risk assessment as opposed to fixed plasma levels.

Strengths of the study are real-world data, causality and severity assessed by standardized criteria, and both clinical and pharmacokinetic risk factors assessed. Limitations of the study in the form of retrospective, single-centre design, limited sample number for blood concentration analysis, and absence of pharmacogenetic information (e.g., CYP2C19 status) limit wider generalizability.

CONCLUSION

Voriconazole treatment in this real-world tertiary care group was characterized by a high frequency (61.1 %) of moderate ADRs, predominantly hepatotoxicity (elevation of aminotransferases). Notably, type 2 diabetes mellitus and cardiovascular comorbidities and thyroid disorders showed a statistically significant association with occurrence of ADRs, the clinical significance of which would be worth exploring.

Prospective multicentre trials with the incorporation of pharmacogenetic information are advised to further explore comorbidity-based risk stratification and streamline individualized dosing protocols. The retrospective, single centre design and small sample size limit broader generalizability. Lack of CYP2C19 genotyping also limits investigation into pharmacogenetic effects on adverse events. In view of these limitations, prospective, multicentre studies incorporating pharmacogenetic profiling with robust pharmacokinetic and clinical monitoring are recommended to further

optimize risk stratification and individualized voriconazole dosing strategies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Akçay Ö, Gümüştekin M. Voriconazole-induced hepatotoxicity concise up-to-date review. J Bas Clin Health Sci. 2022;6(1):325-34.
2. Ertem O, Gümüştekin M. Voriconazole induced hepatotoxicity: concise up to date review. J Basic Clin Health Sci. 2022;6(1):325–34.
3. Groll AH, Noel AA, Warn PA. Neurologic and hepatic adverse effects of voriconazole. Clin Infect Dis. 2004;39(1):124–31.
4. Xu D, Wang H. Unusual voriconazole hepatotoxicity: hepatotoxic reaction at low trough concentration. Infect Drug Resist. 2023;16:1479–87.
5. Zonios DI, Marriet E, Piscitelli SC. Hallucinations during voriconazole therapy. Clin Infect Dis. 2008;47:1–10.
6. Neofytos D, Fishman JA. Neurologic side effects of voriconazole therapy. Clin Infect Dis. 2016;62(3):398–407.
7. Zrenner B. Visual and neurological adverse effects of triazole therapy: impact of CYP2C19 phenotype. Rev Ital Med Lab. 2024;12(2):105–13.
8. World Health Organization. The use of the WHO-UMC system for standardized case causality assessment. Uppsala: The Uppsala Monitoring Centre. 2005: 167.
9. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals. International Committee of Medical Journal Editors. 2015.
10. Ertem MO, Gümüştekin M. Voriconazole-induced hepatotoxicity review: real-world hepatotoxicity rates up to 68%. J Basic Clin Health Sci. 2022;6(1):325–34.
11. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring improves efficacy and safety outcomes. Clin Infect Dis. 2004;39(5):712-9.
12. Park WB, Kim NH, Kim KH. Voriconazole concentrations and outcome in invasive fungal infections: variability limits predictive value. J Antimicrob Chemother. 2013;71(7):1786–93.
13. Lou Y, Wang Y, Liu J, Wang YJ, Wang J, Ma S, et al. Voriconazole-induced liver injury: incidence patterns and risk factors in a retrospective cohort. Antimicrob Agents Chemother. 2025;69(9):487-25.
14. Mohd Sazlly Lim S, Sinnollareddy M, Sime FB. Challenges in Antifungal Therapy in Diabetes Mellitus. J Clin Med. 2020;9(9):2878.

Cite this article as: Nandan A, Palatty PL, Govindraj L. Echoes of adversity with Voriconazole: a retrospective study. Int J Basic Clin Pharmacol 2025;14:931-6.