ORIGINAL ARTICLE

Therapeutic Drug Monitoring of Isavuconazole: Lessons Learnt from a Real-life Setting in a Tertiary Care Center in India

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Abstract

Introduction: Isavuconazole is an emerging therapeutic option for invasive infections caused by molds, especially aspergillosis and mucormycosis. Isavuconazole has predictable pharmacokinetics and good bioavailability. These attributes have led to some doubts regarding the need for therapeutic drug monitoring (TDM). There are no data from India regarding TDM for isavuconazole.

Methods: A retrospective analysis of 50 patients who received oral isavuconazole for therapeutic purposes. Plasma isavuconazole levels were measured using a reversed phase high-performance liquid chromatography (HPLC) and UV detector with acetonitrile (ACN) as protein precipitating solvent.

Results: Of the 50 cases, 5 (10.0%) patients had subtherapeutic levels, while 45 (90.0%) had therapeutic levels. Higher body weight and solid organ transplantation (SOT) were significantly associated with subtherapeutic levels of isavuconazole (p-value < 0.05 for all). Receipt of a SOT was the only independent and statistically significant factor which was associated with subtherapeutic levels of isavuconazole (p-value < 0.05).

Conclusion: Our study reemphasizes the need of TDM for isavuconazole and adds to the growing evidence for the need to obtain drug levels. Factors associated with subtherapeutic levels of isavuconazole need to be assessed in larger studies to help identify those patients who are at risk of having subtherapeutic drug levels.

Keywords: Aspergillosis, Drug monitoring, Fungal infections, Fungus, Isavuconazole, Mold infections, Mucormycosis, Therapeutic drug monitoring.

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Introduction

Isavuconazole is an emerging therapeutic option for invasive infections caused by molds, especially aspergillosis and mucormycosis. For mucormycosis, it is recommended as salvage therapy or when the use of amphotericin is limited by toxicity or underlying renal dysfunction.[1] A double-blind randomized study published in 2016 demonstrated that isavuconazole proved to be non-inferior to voriconazole for treating invasive mold infections.[2] In this study, isavuconazole was well tolerated with very few side effects.[2]

The important enzymes involved in the metabolism of isavuconazole are CYP3A4 and CYP3A5. Isavuconazole has predictable pharmacokinetics and good bioavailability.[3] These attributes have led to some doubts regarding the need for therapeutic drug monitoring (TDM). The 2016 Practice Guidelines for the Diagnosis and Management of Aspergillosis stated that more evidence is needed to determine whether TDM is helpful or necessary for isavuconazole.[4] However, there is evidence to suggest that drug concentrations in the real-life settings can be lower than those attained in trials.[5] Also, the target serum levels need to be individualized for patients depending on factors such as the minimum inhibitory concentrations (MICs) of the mold being treated, in order to achieve the optimal pharmacodynamic target. Though generally well tolerated, with a robust safety profile, there is evidence to suggest that a cutoff threshold for toxicity of 5.13 mg/L should be used.[6]

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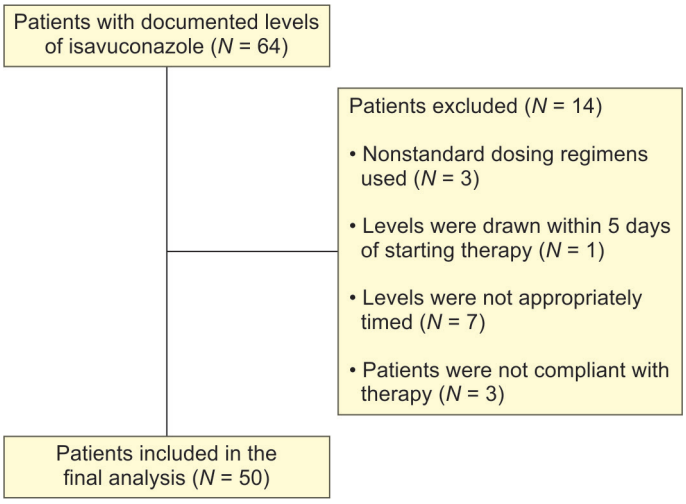
Flowchart 1: Patient enrolment: included 50 patients who received oral isavuconazole for therapeutic purposes. Patients were excluded if levels were drawn within 5 days of starting therapy, patients were taking doses other than the standard recommended dose of oral isavuconazole, if levels were not appropriately timed, or if patients were not compliant with therapy



There are no data from India regarding TDM for isavuconazole. Therapeutic drug monitoring for isavuconazole is available in very few centers across the country. We conducted a retrospective analysis of the plasma isavuconazole levels performed in our tertiary care center in western India. We analyzed the levels to ascertain the proportion of patients who attained adequate levels as well as those who showed signs of drug toxicity or inability to tolerate isavuconazole. We also studied the factors that were related with subtherapeutic levels of isavuconazole.

Methods

Patient Selection

This was a retrospective study of 50 patients who were prescribed oral isavuconazole therapeutically. We excluded patients if the levels were done within 5 days from initiating therapy, patients were receiving oral isavuconazole in doses other than the standard recommended dose, if levels were not appropriately timed, or if patient compliance with the therapy was poor (Flowchart 1). An institutional ethics committee (IEC) approval was obtained before commencing the study. We included only those patients in the analysis, in whom isavuconazole levels were performed as a part of routine management.

Measurement of Isavuconazole Levels

A reversed phase high-performance liquid chromatography (HPLC) and UV detector with acetonitrile (ACN) as protein-precipitating solvent was used to measure the plasma isavuconazole levels. Sensitivity and linearity were 0.25 and 10.0 µg/L with an intra- and inter-assay variation less than 6.12% and 10.34% at 50 µL injection volume, respectively.

Statistical Analysis

The Chi-square test or Fisher's exact probability test was used for the inter-group statistical comparison of distribution of categorical variables. The inter-group statistical comparison of distribution of medians of continuous variables was done using the Mann–Whitney *U* test. Multivariate stepwise logistic regression analysis was performed to obtain the statistically significant and independent determinants of low levels of isavuconazole.

In the entire study, *p*-values less than 0.05 were considered statistically significant. The entire data were statistically analyzed using the Statistical Package for Social Sciences (SPSS version 24.0, IBM Corporation, USA) for MS Windows.

Results

Table 1 demonstrates the distribution of serum isavuconazole levels across the study population. Of the 50 cases studied, 5 (10.0%) patients had subtherapeutic levels, while 45 (90.0%) had therapeutic levels. Table 2 shows the distribution of isavuconazole levels with respect to the demographics, underlying conditions, therapies, and other factors (Univariate statistical analysis). Of the 50 patients studied, 29 were being treated in the intensive care unit (ICU) when the serum isavuconazole levels were drawn. Of the 5 patients who had subtherapeutic levels, 3 (60%) were being treated in the ICU. On univariate statistical analysis, factors such as relatively higher body weight and solid organ transplant (SOT) showed a statistically significant association with subtherapeutic levels of isavuconazole ($p < 0.05$ for all). On multivariate logistic regression analysis (stepwise procedure), receipt of a SOT was the only independent and statistically significant factor which was associated with subtherapeutic levels of isavuconazole, after adjusting for confounders such as age, gender, weight, other indications, and treatment groups ($p < 0.05$) (Table 3). As shown in Table 4, the isavuconazole dose was increased in 11/50 patients after the levels were obtained, as deemed appropriate by the treating physician. Of these, five patients had subtherapeutic levels, three

Table 1: Distribution of isavuconazole levels across the study population

Isavuconazole level	*No. of cases*	*% of cases*
Subtherapeutic (<2.0 mg/L)	5	10.0
Therapeutic (≥2.0 mg/L)	45	90.0
Total	50	100.0

Table 2: Distribution of serum levels of isavuconazole according to demographic characteristics, underlying conditions, therapies, and other factors (univariate statistical analysis)

		Isavuconazole level						
		Subtherapeutic (<2.0 mg/L) (n = 5)		*Therapeutic levels (≥2.0 mg/L) (n = 45)*		*Total (n = 50)*		*p-value*
Demographics		*n*/median	%/range	*n*/median	%/range	*n*/median	%/range	
Age (years)	Median (range)	53.00	29–70	60.00	26–84	57.50	26–84	0.296^{NS}
Male sex	*n* (%)	5	12.8	34	87.2	39	100.0	0.573^{NS}
Weight (kg)	Median (range)	72.00	60–84	60.00	40–99	61.50	40–99	0.046*
BMI (kg/m^2)	Median (range)	26.00	22–29	24.00	17–37	24.00	17–37	0.159^{NS}
Dose (mg/kg)	Median (range)	200.0	200–200	200.0	200–300	200.0	200–300	0.826^{NS}
Underlying conditions								
BMT	*n* (%)	0	0.0	1	100.0	1	100.0	0.999^{NS}
GvHD	*n* (%)	0	0.0	1	100.0	1	100.0	0.999^{NS}
SOT	*n* (%)	2	100.0	0	0.0	2	100.0	0.008**
Diabetes	*n* (%)	3	9.4	29	90.6	32	100.0	0.999^{NS}
COVID-19	*n* (%)	3	8.8	31	91.2	34	100.0	0.650^{NS}
Therapies								
Chemotherapy	*n* (%)	1	25.0	3	75.0	4	100.0	0.353^{NS}
Radiotherapy	*n* (%)	1	25.0	3	75.0	4	100.0	0.353^{NS}
PEG	*n* (%)	0	0.0	1	100.0	1	100.0	0.999^{NS}
Steroids	*n* (%)	3	8.8	31	91.2	34	100.0	0.650^{NS}
Other factors								
PPI	*n* (%)	4	19.0	17	81.0	21	100.0	0.148^{NS}
Diarrhea	*n* (%)	0	0.0	3	100.0	3	100.0	0.999^{NS}
Mucositis	*n* (%)	0	0.0	2	100.0	2	100.0	0.999^{NS}
Adverse effects								
Hypokalemia	*n* (%)	0	0.0	1	2.2	1	2.0	0.999^{NS}
GI disturbance	*n* (%)	1	20.0	4	8.9	5	10.0	0.423^{NS}
Deranged LFTs	*n* (%)	1	20.0	0	0.0	1	2.0	0.100^{NS}
Headaches	*n* (%)	1	20.0	2	4.4	3	6.0	0.276^{NS}

p-value for age, weight, BMI, and dose by the Mann–Whitney *U* test; the rest of the *p*-values by Chi-square or Fisher's exact probability tests. *p*-value <0.05 has been considered to be statistically significant; **p*-value <0.05, ***p*-value <0.01, ^{NS}, statistically nonsignificant

had baseline levels between 2 and 3 mg/L, and three patients had baseline drug levels ≥3.0 mg/L.

Discussion

Isavuconazole is emerging as an effective option for treating invasive aspergillosis as well as salvage therapy or step-down therapy for mucormycosis. There are some doubts regarding whether TDM is required for isavuconazole. The Dutch Working Party on Antibiotic Policy (SWAB) recommendations for the diagnosis and management of COVID-19 associated pulmonary aspergillosis recommend levels between 2 and 4 mg/L for patients being treated with isavuconazole.[7] A study assessing the isavuconazole blood levels and their relation with the toxicity and efficacy found isavuconazole levels of 2.86 mg/L after 14 days of therapy and 4.4 mg/L after 42 days in patients who had response to therapy. Based on this, the authors recommended targeting levels of >2.5 mg/L while using isavuconazole in a therapeutic setting.[6]

Using a cutoff of 2 mg/L, we found that 10% of the patients in our study had subtherapeutic serum levels of isavuconazole when they were being administered the oral preparation. This is significant, and shows why TDM is essential. Also, dose modification may be required in certain patients, keeping in mind the pharmacodynamic targets for isavuconazole. This depends on the type of fungal infection being treated, the species, the MICs, as well as the site of infection. Based on a murine model of invasive aspergillosis, for a survival rate of 50%, the effective AUC_{0-24}/MIC_{CLSI} ratio for isavuconazole total drug was found to be 50.48 (95% confidence interval, 44.90–56.74).[8] Buil et al.[9] found a strong correlation between isavuconazole levels and AUC_{0-24}. It was suggested that the relationship between the parameters could be described as $AUC_{0-24} = 10.2 + 24.48\ C_{trough}$.[9] In the same study, the probability

Table 3: Multivariate logistic regression analysis for finding the independent determinants of subtherapeutic levels of isavuconazole

Risk factors (variables in the model after stepwise procedure)		*Odds ratio (OR)*	*95% CI for odds ratio*	*p-value*
Body weight (kg)	<61.5 (median)	1.00	–	–
	≥61.5	1.69	0.87–3.52	0.102[NS]
SOT	Absent	1.00	–	–
	Present	2.22	1.02–4.09	0.016[*]

Odds ratio = 1: reference category. Dependent variable: subtherapeutic levels of isavuconazole; *p-value <0.05, [NS], statistically nonsignificant

Table 4: Patients in whom the isavuconazole dose was changed after levels were obtained

	Levels <2.0 mg/L	*Levels between 2.0 and 3.0 mg/L*	*Levels ≥3.0 mg/L*
Total number of patients	5	10	35
Of these, the number of patients in whom the dose of isavuconazole was increased after levels were obtained	5	3	3

of target attainment for 90% effective concentration (EC90), for isolates with an MIC of 2 mg/L increased from 64–92% when the daily dose was increased from 200–400 mg.[9] This shows that it is important to individualize dosing strategies and the target drug levels to optimize the pharmacodynamics. In our study, 11 out of the 50 patients (22%), the dose of isavuconazole was increased after obtaining levels as deemed appropriate by the treating physician. This again emphasizes the need for TDM in patients receiving isavuconazole therapy. This becomes especially vital when treating infections with isolates having MICs > 1 mg/L.

In our study, on univariate analysis, relatively higher weight and SOT were factors which were associated with subtherapeutic levels of isavuconazole. On multivariate analysis, SOT was found to be associated with subtherapeutic levels. Recipients of SOT receive multiple other drugs including immunosuppressants, and TDM becomes even more vital in this patient population.

In a phase 3, double-blinded, global multicentric, comparative-group study of patients with invasive mold disease, isavuconazole was better tolerated compared to voriconazole. In a study which included patients with chronic pulmonary aspergillosis, the mean drug level at the first measurement was 5.5 ± 2 mg/L for patients reporting adverse events (AEs), compared with 4.2 ± 1.7 mg/L for those not reporting AEs (p = 0.032).[10] In our study, 5 out of the 50 patients experienced at least one side effect related to isavuconazole. Most of these were minor (all five had minor gastrointestinal disturbances, one had hypokalemia, one had mild transaminitis, and three had headaches). These side effects did not seem to be dependent on the levels of isavuconazole in our study. In general, isavuconazole was well tolerated with minimal adverse effects in our study. Isavuconazole has been found to have minimal toxicity in published literature, though Furfaro et al.[6] suggested a cutoff threshold for toxicity of 5.13 mg/L. Thus, when required for pharmacodynamic optimization, isavuconazole doses can be safely increased up to drug levels of 4–5 mg/L.

Limitations

The sample size is relatively small, and hence, factors associated with subtherapeutic levels need to be assessed in larger studies. Also, most patients in whom the dose of isavuconazole was increased did not undergo repeat TDM. And hence, the effects of increased dosing could not be accurately assessed. The adverse effects were recorded retrospectively through electronic health records, and hence, it is possible that some minor adverse effects were missed.

Conclusion

This is the first study from India describing the experience of TDM for isavuconazole in a real-world scenario. Our study reemphasizes the need of TDM for isavuconazole and adds to the growing evidence for the need to obtain drug levels. It also shows that isavuconazole is generally well tolerated. Receipt of SOT was found to be associated with subtherapeutic levels in our study. Factors associated with subtherapeutic levels of isavuconazole need to be assessed in larger studies to help identify those patients who are at risk for having subtherapeutic drug levels.

Ethical Approval Statement

An approval was granted by the IEC prior to starting the study.

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