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Factors associated with subtherapeutic levels of oral posaconazole tablet: a detailed analysis from a tertiary care center in India

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ABSTRACT

Objectives: Posaconazole is a broad-spectrum triazole antifungal, with activity against various clinically important fungi. The delayed release (DR) tablet of posaconazole has been shown to have a superior pharmacokinetic profile in comparison with the oral suspension.
Methods: We retrospectively analyzed the factors associated with posaconazole levels <1.25 μg/ml in 164 patients receiving the DR tablet for therapeutic purposes.
Results: Of the 164 patients, 53 (32.3%) showed subtherapeutic trough levels of posaconazole. The use of proton pump inhibitors (95% CI 1.41-3.91; *P*-value = 0.028) and the presence of diarrhea (95% CI 1.95-6.93; *P*-value = 0.001) were significantly associated with subtherapeutic levels. A total of 13 of the 21 patients receiving posaconazole tablets through a nasogastric tube had therapeutic levels.
Conclusion: This is the largest study from India that analyzed factors associated with subtherapeutic levels of the DR tablet of posaconazole. These findings reinforce the importance of therapeutic drug monitoring. Unlike in previous studies, obesity and hypoalbuminemia were not found to be significant factors in our settings. The use of proton pump inhibitors and diarrhea remained significant factors, as found in previous studies. Administering the DR tablet of posaconazole through a nasogastric tube may be a viable option.

Introduction

Posaconazole is a broad-spectrum triazole antifungal with potent activity against various clinically important fungal organisms. The delayed release (DR) tablet of posaconazole has been shown to have a superior pharmacokinetic profile in comparison with the oral suspension. A retrospective analysis in 2015 showed that 91% of the patients receiving the DR tablet had posaconazole trough levels of more than 700 ng/ml, against 61% of those receiving the oral suspension (Durani *et al.*, 2015). Furthermore, in this study, the median posaconazole trough levels in patients receiving the DR tablet were more than twice than that of the suspension cohort (Durani *et al.*, 2015). Studies have suggested that the absorption of the DR tablets is not extensively affected by food (Krishna *et al.*, 2012). Administration of the tablet does not require concomitant ingestion of carbonated beverages, unlike with the oral suspension. A retrospective analysis of patients receiving the DR posaconazole tablet for prophylaxis showed that patients were more likely to have subtherapeutic troughs if they had diarrhea, were receiving a proton pump inhibitor (PPI), or weighed >90 kg (Tang *et al.*, 2017). The authors concluded that although the tablet produced more consistent levels, there is still a need for therapeutic drug monitoring.

Posaconazole is not metabolized through the cytochrome P450 enzyme system. About 15-17% of the drug undergoes noncytochrome P450-based metabolism, primarily through phase two biotransformations, using uridine diphosphate glucuronosyltrans-

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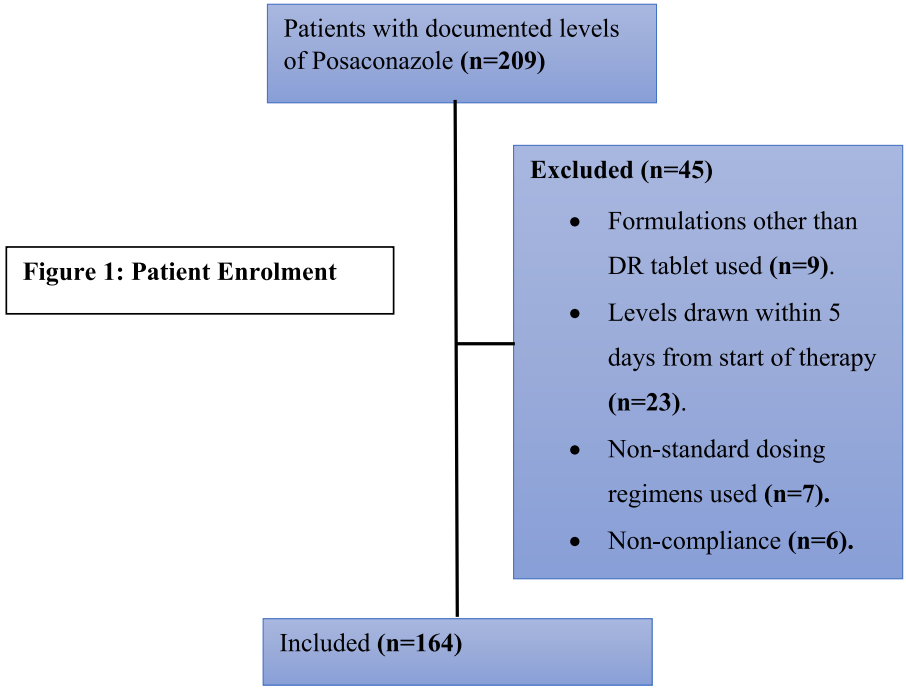

Figure 1: Patient Enrolment

Figure 1. Patient enrollment.
Abbreviation: DR, delayed release.

ferase enzyme pathways. Hence, inhibitors or inducers of these pathways may influence the drug levels of posaconazole (Li *et al.*, 2010). A small retrospective analysis of 29 patients from India showed that 24.1% had subtherapeutic levels of posaconazole (Patel *et al.*, 2022). However, larger studies from India are unavailable, and the effect of uridine diphosphate glucuronosyltransferase polymorphisms in our population remains unknown.

There are sparse data regarding the pharmacokinetics of DR posaconazole tablets administered through a nasogastric (NG) tube. In a small case series, two of the four patients showed suboptimal levels of posaconazole when crushed tablets were administered through an NG tube (Mason *et al.*, 2019). However, larger studies on the administration of posaconazole through a feeding tube are unavailable.

Posaconazole levels of more than 700 ng/ml have been recommended in the prophylactic setting. However, in the therapeutic setting, higher levels are required. Pharmacodynamic targets are based on the ratio of the area under the curve (AUC) to the minimum inhibitory concentration (MIC) (AUC/MIC ratio). Levels of more than 1-1.25 μg/ml are recommended for therapeutic purposes (Dolton *et al.*, 2012; Seyedmousavi *et al.*, 2013).

We analyzed the factors associated with posaconazole levels $<$1.25 μg/ml in patients who were receiving the DR tablet for therapeutic purposes.

Methods

We conducted a retrospective analysis of 164 patients who were receiving the DR tablet for therapeutic purposes. For patients taking the DR tablet of posaconazole, the dose administered was 300 mg twice a day on the first day, followed by 300 mg daily from the second day. Patients were excluded if levels were drawn within 5 days of starting therapy, if levels were inappropriately timed, if the patients received formulations other than the DR tablet, or if patients were not compliant with therapy (Figure 1).

The data were collected from the hospital electronic records. Serum posaconazole levels were measured using the high-performance liquid chromatography method with ultraviolet detection, with an injection volume of 50 µl (Sengar *et al.*, 2016). Inter- and intra-assay precision were 6.45% and 5.18%, respectively, for posaconazole. Subtherapeutic levels were defined as $\leq$1.25 μg/ml. Cases with subtherapeutic levels were compared with controls, having levels $\geq$1.25 μg/ml. Various factors were compared based on the existing literature on serum trough concentrations of posaconazole.

An approval was obtained from the institutional ethics committee before the initiation of the study. Only those patients in whom posaconazole levels were obtained as a part of their management were included in the study.

Statistical analysis

The intergroup statistical comparison of distribution of categorical variables was done using the chi-square test or Fisher's exact probability test. The intergroup statistical comparison of distribution of medians of continuous variables was done using the Mann-Whitney *U* test. Multivariate stepwise logistic regression analysis was used to obtain the statistically significant and independent determinants of low levels of posaconazole. The underlying normality assumption was tested before subjecting the study variables to the Mann-Whitney *U* test. In the entire study, a *P*-value of less than 0.05 was considered to be statistically significant. The data were statistically analyzed using the Statistical Package for Social Sciences (SPSS version 22.0, IBM Corporation, USA).

Results

A total of 164 patients were studied. Of these, 53 (32.3%) had subtherapeutic levels of posaconazole, and 111 (67.7%) had therapeutic levels.

Table 1 shows the distribution of demographic characteristics, underlying conditions, and other factors according to the levels of posaconazole (univariate statistical analysis). Patients with subtherapeutic levels of posaconazole were younger, with a median age

Table 1
Distribution of demographic characteristics, indications and treatments according to level of posaconazole (Univariate statistical analysis).

Demographics		Posaconazole level						*P*-value
		Subtherapeutic levels (n=53)		Therapeutic levels (n=111)		Total (n=164)		
		n / median	%/range	n / median	%/range	n / median	%/range	
Age (years)	Median (Range)	48.67	7.0-82.7	53.25	16.2-82.7	51.50	7.0-82.7	0.006**
Male sex	n (%)	35	28.0	90	72.	125	100.0	0.034*
Weight (kg)	Median (Range)	65.50	20-92	65.00	38-100	65.00	20-100	0.437^{NS}
BMI (kg/m^2)	Median (Range)	24.00	12-37	24.00	14-36	24.00	12-37	0.480^{NS}
Underlying conditions								
AML	n (%)	10	76.9	3	23.1	13	100.0	0.001***
ALL	n (%)	2	66.7	1	33.3	3	100.0	0.244^{NS}
BMT	n (%)	8	80.0	2	20.0	10	100.0	0.002**
GVHD	n (%)	5	83.3	1	16.7	6	100.0	0.014*
SOT	n (%)	0	0.0	0	0.0	0	0.0	–
Diabetes	n (%)	22	23.7	71	76.3	93	100.0	0.007**
COVID-19	n (%)	34	25.4	100	74.6	134	100.0	0.001***
Therapies								
Chemotherapy	n (%)	14	70.0	6	30.0	20	100.0	0.001***
Steroids	n (%)	42	31.1	93	68.9	135	100.0	0.476^{NS}
Other factors								
PPI	n (%)	27	50.0	27	50.0	54	100.0	0.001***
Diarrhea	n (%)	16	94.1	1	5.9	17	100.0	0.001***
PEG tube feeding	n (%)	1	50.0	1	50.0	2	100.0	0.543^{NS}
Nasogastric tube feeding	n (%)	8	38.1	13	61.9	21	100.0	0.544^{NS}
Mucositis	n (%)	7	100.0	0	0.0	7	100.0	0.001***
Serum Albumin levels	Median (Range)	3.07	1.81-4.7	3.11	1.58-4.67	3.1	1.58-4.7	0.756

P-value for age, weight, BMI and dose by Mann-Whitney U test; the rest of the *P*-values by Chi-Square test. *P*-value<0.05 is considered to be statistically significant. *P-value<0.05, **P-value<0.01, ***P-value<0.001, NS - statistically non-significant.
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index; BMT, bone marrow transplantation; GVHD, graft versus host disease; PEG, percutaneous endoscopic gastrostomy; PPI, proton pump inhibitor; SOT, solid organ transplantation.

Table 2
Analysis of posaconazole levels, when posaconazole was administered using an NG or PEG tube.

Method of posaconazole administration	Number of patients	Number of patients with therapeutic levels (%)	Median levels, μg/ml (range)	Remarks
NG tube	21	13 (61.9)	1.48 (0 - 4.01)	
PEG tube	2	1 (50)	-	1 patient had a level of 0.81 μg/ml, while the other had a level of 7.54 μg/ml

Abbreviations: NG, Nasogastric; PEG, percutaneous endoscopic gastrostomy.

of 48.67 years versus 53.25 years in the therapeutic group. The presence of acute myeloid leukemia, bone marrow transplantation, graft versus host disease, chemotherapy, PPIs, diarrhea, or mucositis were all associated with subtherapeutic levels of posaconazole on univariate analysis. There was no significant difference in the albumin levels between the two groups.

Table 2 shows the posaconazole levels in patients who were administered posaconazole either using a percutaneous endoscopic gastrostomy (PEG) tube or using an NG tube. More than half of the patients had therapeutic levels of posaconazole when administered using an NG tube (Table 3).

On the multivariate logistic regression analysis (stepwise procedure), diarrhea and PPI were the independent and statistically significant factors associated with a low level of posaconazole after adjusting for age, sex, acute myeloid leukemia, bone marrow transplantation, graft versus host disease, chemotherapy, and mucositis (*P*-value <0.05).

Discussion

Although studies have shown that the DR tablet formulation of posaconazole is associated with more appropriate levels of the drug (Durani *et al.*, 2015), 32.3% of the patients in this study had levels less than the desired therapeutic concentrations. This is significant, given the pharmacodynamic targets for posaconazole for treating mold infections. Howard *et al.* reported that an AUC/MIC ratio of more than 167 was associated with half-maximal activity in murine models of pulmonary aspergillosis, assessed by reductions in serum galactomannan levels (Howard *et al.*, 2011). Lepak *et al.* reported that an AUC/MIC ratio of 109 was associated with the suppression of lung fungal burden in animals infected with *Aspergillus fumigatus* (Lepak *et al.*, 2013). Lewis *et al.* noted that in murine models of invasive pulmonary aspergillosis and mucormycosis, when an AUC/MIC target of >100 was used, it correlated with minimum serum posaconazole concentrations of 1.25 mg/l for

Table 3
Multivariate logistic regression analysis for finding the independent determinants of low levels of posaconazole.

Risk factors (Variables in the model after stepwise procedure)		OR	95% CI for OR	*P*-value
PPI	Absent	1.00	–	–
	Present	2.45	1.41-3.91	0.028*
Diarrhea	Absent	1.00	–	–
	Present	3.89	1.95-6.93	0.001***

OR = 1: Reference category.
Dependent variable: Low level of posaconazole,
* *P*-value<0.05,
*** *P*-value<0.001.Abbreviations: OR, Odds ratio; PPI, proton pump inhibitor.

aspergillosis and 4.0 mg/l for the model of mucormycosis (Lewis *et al.*, 2014). These studies show that it is critical to have optimum therapeutic levels of posaconazole to maximize the chances of reaching the pharmacodynamic target. Nearly one-third of the patients in our study fell short of achieving the minimum recommended therapeutic levels. Higher doses of posaconazole had to be eventually used in these patients.

Previous studies have shown that subtherapeutic posaconazole levels can be associated with the use of PPIs, diarrhea, and weight >90 kg (Tang *et al.*, 2017). In our study, we found that on multivariate analysis, the use of PPIs and diarrhea were associated with subtherapeutic levels of posaconazole. A number of patients who undergo chemotherapy or those who receive a bone transplant can develop diarrhea. When posaconazole is used for therapeutic purposes in such patients, the possibility of subtherapeutic levels need to be borne in mind because these patients may need higher than the standard recommended dose of the DR posaconazole preparation to meet the desired pharmacodynamic targets. Furthermore, the overzealous use of PPIs needs to be avoided in patients on posaconazole therapy. In our setup, we did not find obesity to be a significant factor associated with subtherapeutic levels, unlike Tang *et al.,* who found that weight >90 kg was associated with subtherapeutic levels (Tang *et al.*, 2017).

Another important finding in our study was that the use of enteral feeding tubes was not associated with subtherapeutic levels of posaconazole. A total of 61.9% of the patients who received posaconazole for therapeutic purposes through an NG tube achieved therapeutic levels, and the median level of the drug in these patients was 1.48 μg/ml. One of the two patients who received posaconazole using a PEG tube had therapeutic levels. There is sparse literature regarding this, and Mason *et al.* have described four patients who were administered crushed posaconazole tablets (Lewis *et al.*, 2014). In their study, two of the four patients achieved therapeutic levels of the drug (Lewis *et al.*, 2014). Our study showed that crushed tablets of posaconazole can be administered using NG or PEG tubes. However, therapeutic drug monitoring is important in these patients. A retrospective study of 242 cases demonstrated that hypoalbuminemia was associated with subtherapeutic levels in patients receiving the posaconazole tablet (Mason *et al.*, 2019). However, in our study we did not find hypoalbuminemia to be a significant factor associated with subtherapeutic factors.

Limitations

There are some limitations to our study. Owing to the retrospective nature of the study, there was no quantification of the diarrhea. Furthermore, only two patients included in this study received PEG tube feeding; hence, definitive conclusions could not be drawn, although there were 21 patients who received posaconazole using an NG tube.

Conclusion

This is the largest study from India that analyzed the serum posaconazole levels in patients receiving the DR tablet for therapeutic purposes. Our study reinforces the fact that even with the DR tablet, some patients may still achieve suboptimal drug levels; hence, optimal levels need to be obtained for all patients, especially when posaconazole is being used for therapeutic purposes. Our study shows that diarrhea and the concomitant use of PPIs are associated with subtherapeutic levels of posaconazole. However, obesity or low serum albumin levels do not seem to be factors associated with subtherapeutic levels in our settings. In addition, our study shows that administration using an NG tube can be a reasonable alternative in patients; however, drug levels need to be checked in these patients.

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Declaration of competing interests

The authors have no competing interests to declare.

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