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Letter to the Editor

Comparative analysis of serum and sebum concentration of super-bioavailable itraconazole 50 versus 65 mg in healthy adult volunteers

Sir,

Super-bioavailable itraconazole (SBITZ) is a new form of itraconazole which overcomes the pharmacokinetic issues of conventional itraconazole (CITZ). Currently two strengths are approved globally for SBITZ; 50 mg and 65 mg which exhibit greater bioavailability than CITZ and widely prescribed in systemic mycosis and dermatophytosis.[1] Though both the strengths have proven to be bioequivalent with CITZ 100 mg but difference was reported in achieving therapeutic concentration of ITZ in patients.[2,3] Secondly, skin kinetics study in terms of sebum concentration is lacking for both the strengths.

Since SBITZ is commonly prescribed in dermatophytosis in India, assessment of sebum levels plays important role for treatment outcome which is correlated with serum levels (trough concentration) of ITZ. Hence, current study was planned to evaluate the serum and sebum concentration achieved by both strengths in Indian healthy adult volunteers.

After independent ethics committee approval, twenty healthy volunteers were enrolled and divided equally into 2 groups with duration of study being 14 days. Group I received SBITZ 65 mg (SB 65) twice daily while group II received SBITZ 50 mg (SB 50) twice daily after food. Trough concentration was evaluated on day 1, 3, 7 and 14 while sebum concentration was evaluated on day 7 and day 14. Serum concentration was analyzed by high performance liquid chromatography (HPLC) method by inserting IV catheter into forearm vein.[4] Sebum concentration was analyzed by paper absorption method wherein pre-weighed rolling flax paper (OCB, France) was held over the demarcated area on forehead for 3 hours and post-test, the paper was weighed again to determine the quantity of the sebum.[5]

For both the strengths, serum concentration was found to increase gradually from day 1 onwards till day 14. But trough concentration of day 7 and 14 were considered for analysis as itraconazole had shown to achieve steady state concentration as early as 7 days.[6] SB 65 was found to be statistically significant than SB 50 in achieving trough concentration at day 14 as shown in Table 1. Similarly, sebum concentration was also statistically significant ($p<0.05$) for SB 65 against SB 50 on both days (Table 1). In SB 50 group, 3 volunteers failed to achieve therapeutic concentration of ITZ (>1000 ng/ml) as compared to one patient in SB 65 group at end of 14 days.

Table 1: Trough concentration and sebum concentration of SB 50 and SB 65 at day 7 and 14.

Subject no.	Trough concentration of ITZ (ng/ml)					Sebum concentration of ITZ (ng/mg)				
	Day 7		Day 14		P value	Day 7		Day 14		P value
	SB 50	SB 65	SB 50	SB 65		SB 50	SB 65	SB 50	SB 65	
1	1215	1245	1470	1475	<0.05*	970	1080	975	1220	<0.05#
2	1150	1268	1280	1390		1010	1010	1230	1140	
3	1340	1590	1390	1730		880	1160	945	1320	
4	1380	1370	1460	1468		800	1095	1008	1210	
5	920	1396	960	1475		950	1050	1050	1100	
6	1430	1400	1470	1590		970	1120	1089	1110	
7	1213	957	1350	980		1118	920	1145	965	
8	965	1410	970	1600		850	1100	960	1268	
9	1280	1380	1320	1493		1022	1008	980	1170	
10	960	1395	990	1570		1045	990	1050	1098	

*Statistical significant at day 14 only, #statistical significant at day 7 and 14.

In the current scenario for management of dermatophytosis in India, ITZ remains a useful antifungal agent, along with topical treatment, but its usefulness is hindered by its inherent pharmacokinetic shortcomings, leading to inconsistent therapeutic concentrations. A newer formulation of SBITZ has shown more reliable attainment of therapeutic concentration compared with older formulations of CITZ and is approved by drugs controller general of India (DCGI) in invasive mycosis in the strength of 50 and 65 mg. The availability of two strengths had created some dilemma at physicians' level regarding prescription and hence this study was performed to evaluate trough concentration and correlate with sebum concentration for both strengths.

Earlier, SB 65 had shown relative bioavailability of 1.82 times than CITZ as compared to 1.73 times with SB 50.[1-3] Moreover, percentage of patients achieving therapeutic concentration with SB 65 was 81% as compared to 69% in SB 50.[2,3] In our study as well, 90% of the volunteers achieved therapeutic concentration in SB 65 as compared to 70% in SB 50. As per one study, C_{trough} ITZ levels should be between 1,000 and 2,000 ng/ml for treatment and >500 ng/ml for prophylaxis against deep mycosis.[3] However, Khurana et al has mentioned cut off value as 200 ng/ml for ITZ in the management of dermatophytosis but with limitation of smaller sample size and single time estimation of ITZ trough levels.[7]

ITZ, being lipophilic in nature, its route of distribution is dependent on sebum and hence determination of sebum concentration becomes critical.[8] Cauwenbergh et al reported ITZ levels in sebum, 2 and 5 times higher than serum levels in back and beard area respectively but with 3 patients only and lack of cut off value for sebum concentration.[6] Though sebum concentration of SB 65 was statistically significant than SB 50 in our study, but due to lack of reference levels for determination of sebum concentration of ITZ, it was difficult to predict preference of one strength over the other. Another limitation lies with shorter duration of study.

CONCLUSION

In conclusion, SB 65 was found to be statistically significant than SB 50 in achieving serum and sebum concentration and could be considered as one of the therapeutic options in dermatophytosis management. Most importantly, to correlate with this concept, large level comparative clinical studies along with determination of MIC and skin kinetics are required. A comparative clinical study with SBITZ 50 mg and 65 mg (CTRI/2022/05/042655) is under way to evaluate safety and efficacy in dermatophytosis.

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