

Topical Itraconazole Formulations: Unscrupulous Pharmaceutical Companies and Lax Indian Drug Regulators Endangering a Precious Drug

The menace of fixed drug combination (FDC) creams and its association with chronic, recalcitrant dermatophytosis (tinea) in India has been documented by Indian dermatologists since 2014.^[1-3] The laxity of Indian regulatory authorities in issuing manufacturing and marketing licenses, general practitioners (GP) prescribing such irrational and hazardous FDCs, their promotion by pharmacists, and self-medication by the public have been the bane of dermatologists who are bearing the brunt of vitiated cases of tinea owing to their rampant use.^[4,5] Most FDCs are combinations of two, three, and even four drugs viz. one antifungal agent, namely, miconazole, clotrimazole, ketoconazole, terbinafine, or itraconazole; a potent corticosteroid, the commonest being clobetasol propionate; and one or two antibacterial agents like neomycin, gentamycin, iodochlorohydroxyquinoline, etc.^[3] Drugs like ofloxacin and ornidazole that are rarely, if ever, used topically have been combined with terbinafine and clobetasol propionate (The “COOT” combination) to create one of the most egregious FDCs ever to be marketed in India or any other country in the world. Notably, such quadruple combinations were deemed irrational by the Drug Controller General of India (DCGI) based on the opinion of an expert advisory committee formed by him in 2018.^[6,7] Following the recommendation for a ban, the moving annual total (MAT) value of the COOT FDC has witnessed a nosedive from INR 279 crores in April 2018 to INR 169 crores in 2019 to INR 40 crores in April 2020. However, scarcely had dermatologists and drug activists stopped rejoicing over the decision of the authorities to ban quadruple combinations,

many pharmaceutical companies managed to obtain illegal permissions to manufacture multiple topical formulations of another purely systemic drug, itraconazole. This development is potentially even more disastrous than the marketing of the COOT FDC in this country, with its ongoing epidemic of recalcitrant tinea.

The most irrational and dangerous of these itraconazole-containing creams is an FDC comprising itraconazole, clobetasol propionate, ornidazole, and ofloxacin. It has the same ingredients as the COOT combination, except that the terbinafine in it has been replaced by itraconazole, a phenomenon reminiscent of the mythical multiheaded *Hydra* [Figure 1]. Like its predecessor, it does not have the mandatory marketing permission which is obtained upon submission of safety and efficacy data from the DCGI. Companies are known to short circuit the system and illegally obtain permission from licensing authorities of individual states of the country. Examining the packaging of these creams reveals that manufacturing licenses for these combinations are usually issued from Uttarakhand, Himachal Pradesh, and Punjab where most of the manufacturing units are situated. It is a small relief that this fledgling FDC is till now being marketed predominantly by obscure, small companies that are unfamiliar to many. Such companies are known to try and capture markets in relatively undeveloped villages and small towns where there is a dearth of legitimate dermatologic care. They primarily approach pharmacists and GPs, many of whom are grossly inadequately trained, to popularize their products. One of the authors has interestingly seen several cases of chronic

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recalcitrant dermatophytosis after the COVID-19 lockdown period in patients who were self-medicating with the FDC in question for weeks upon the recommendation of neighboring pharmacists. The market for this combination is too small yet to be picked up by human data science analytics companies but the very fact that manufacturers of such products have successfully obtained licenses from state drug authorities is a harbinger of further troubles.

Another little-noticed development is the illegal manufacturing and sale of topical itraconazole as a single molecule gel formulation [Figure 2]. An FDC cream of itraconazole and terbinafine has also been unearthed of which an illegal oral formulation already exists [Figure 3]. This FDC is showing a steady growth trend from a MAT of INR 15,00,000 in June 2018 to INR 47,00,000 in June 2020. Companies are also manufacturing shampoos, soaps, and talcum powders containing itraconazole [Figure 4a-c] which are advertised on the net and sold by internet pharmacies.^[8] The use of topical itraconazole and its FDCs, self-medication, erratic application, and absence of quality control can have grave consequences including the induction of itraconazole resistance in the fungal species responsible for the ongoing epidemic of dermatophytosis in India. This recently noticed growth of various formulations of topical itraconazole must be checked immediately for its brazen illegality in addition to the reasons mentioned above.

Indian Association of Dermatologists, Venereologists, and Leprologists (IADVL), the official association comprising 11,000 Indian dermatologists has been making repeated representations to functionaries of the Health Ministry of the Indian Government to discontinue and even ban many such FDCs. Public interest litigation demanding a ban on irrational and hazardous FDCs has been filed by IADVL in the High Court of Delhi. The IADVL Taskforce against Topical Steroid Abuse (ITATSA) has through the association questioned how innumerable completely irrational new FDCs get easy approvals from state licensing authorities, who are not legally allowed to approve any new drug or FDC. The wanton use of potent and super potent topical corticosteroids in these FDCs causes severe local as well as systemic side effects and also suppresses local immunity.^[9]

The deleterious role of FDCs containing antifungals and potent topical corticosteroids in the ongoing epidemic-like scenario of chronic recalcitrant dermatophytosis in India cannot be denied.^[3,10-14] It has also been hypothesized that the potent steroid along with antifungal antibacterial agents alters the cutaneous microbiome.^[14] This may be one of the factors responsible for the rather sudden epidemiologic shift from *Trichophyton rubrum* to *T. mentagrophytes* ITS genotype VIII as the predominant causative species of tinea in India.^[14]

It appears strange that even respectable pharmaceutical companies who employ physicians and microbiologists do



Figure 1: FDC containing itraconazole, clobetasol propionate, and irrelevant antibacterial agents

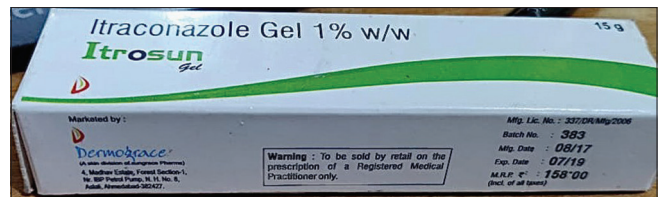


Figure 2: Itraconazole gel



Figure 3: FDC containing itraconazole and terbinafine

not pay heed to the fact that the antifungal drugs act on only a limited number of fungal cellular targets.^[15] Inappropriate selection of antifungal agents in addition to inadequate dose and duration of therapy can result in a partial response or rapid recurrence of infection.^[16] Moreover, the long-term, especially erratic and unsupervised use of topical antifungal agents has a strong potential to contribute to the development of antifungal resistance.^[9,16]

India has also witnessed the waning efficacy of terbinafine as an antifungal molecule over the past 5–7 years. Multiple studies from India and across the globe have documented high MIC values of terbinafine caused by squalene epoxidase mutations in this strain of *T. mentagrophytes*^[17-22] [Table 1]. Though studies regarding antifungal susceptibility patterns for itraconazole are few in comparison to terbinafine, several do point to itraconazole having an edge over other antifungals available in the Indian market.^[17,18] With such a

Table 1: MICs of antifungal agents in the current Indian scenario of dermatophytosis

References	Year	Organism	Drug	MIC 50 (mg/L)	MIC 90 (mg/L)	
Shaw et al. ^[17]	2020	<i>Trichophyton mentagrophytes/T. interdigitale</i> complex	Miconazole	0.03	0.25	
			Luliconazole	0.03	0.125	
			Fluconazole	4	16	
			Itraconazole	0.06	0.25	
			Voriconazole	0.06	0.25	
			Ketoconazole	0.125	0.5	
			Clotrimazole	0.25	0.5	
			Sertaconazole	0.125	0.5	
			Naftifine	0.03	8	
			Terbinafine	0.03	8	
			Griseofulvin	16	32	
			Amorolfine	0.015	0.06	
			Ciclopirox olamine	0.25	0.5	
Ebert et al. ^[18]	2020	<i>T. mentagrophytes</i>	Itraconazole	0.125	0.25	
			Voriconazole	0.0625	0.5	
		<i>T. rubrum</i>	Itraconazole	0.125	0.5	
Maurya et al. ^[19]	2019	<i>T. mentagrophytes</i>	Voriconazole	0.0312	0.5	
			Fluconazole	4	16	
			Itraconazole	0.125	0.25	
		<i>T. rubrum</i>	Ketoconazole	0.06	0.125	
			Terbinafine	2	4	
			Fluconazole	4	32	
			Itraconazole	0.125	0.25	
			Ketoconazole	0.06	0.06	
			Terbinafine	0.3	0.06	
		<i>T. tonsurans</i>	Fluconazole	8	64	
			Itraconazole	0.03	0.06	
			Ketoconazole	0.03	0.06	
			Terbinafine	4	8	
			<i>T. verrucosum</i>	Fluconazole	8	16
				Itraconazole	0.03	0.06
		Ketoconazole		0.125	0.5	
		<i>Microsporium gypseum</i>	Terbinafine	8	16	
			Fluconazole	2	32	
			Itraconazole	0.06	0.125	
			Ketoconazole	0.06	0.125	
			Terbinafine	0.06	0.125	
<i>Epidermophyton floccosum</i>	Fluconazole		1	32		
	Itraconazole	0.03	0.06			
	Ketoconazole	0.06	0.125			
	Terbinafine	0.06	0.125			
	<i>T. violaceum</i>	Fluconazole	8	8		
		Itraconazole	0.03	0.03		
Ketoconazole		0.25	0.25			
Terbinafine		0.25	0.25			
Rudramurthy et al. ^[20]		2018	<i>T. mentagrophytes/T. interdigitale</i> complex	Fluconazole	4	16
				Ketoconazole	0.125	0.5
	Sertaconazole			0.125	0.5	
	Clotrimazole			0.25	0.5	
	Voriconazole			0.125	0.5	
	Itraconazole			0.125	0.5	
	Terbinafine			0.03	4	
	Naftifine			0.0312	8	

Contd...

Table 1: Contd...

References	Year	Organism	Drug	MIC 50 (mg/L)	MIC 90 (mg/L)
		<i>T. rubrum</i>	Amorolfine	0.0156	0.0625
			Ciclopirox olamine	0.25	0.25
			Griseofulvin	32	64
			Luliconazole	0.0312	0.125
			Fluconazole	4	8
			Ketoconazole	0.125	0.5
			Sertaconazole	0.125	1
			Clotrimazole	0.25	0.5
			Voriconazole	0.0625	0.25
			Itraconazole	0.0625	0.25
			Terbinafine	0.015	2
			Naftifine	0.0312	1
			Amorolfine	0.0312	0.0625
			Ciclopirox olamine	0.25	0.25
		<i>T. tonsurans</i>	Griseofulvin	32	128
			Luliconazole	0.0312	0.125
			Fluconazole	4	4
			Ketoconazole	0.125	0.25
			Sertaconazole	0.25	0.25
			Clotrimazole	0.25	0.5
			Voriconazole	0.0625	0.0625
			Itraconazole	0.125	0.25
			Terbinafine	0.5	2
			Naftifine	0.0312	0.125
			Amorolfine	0.0156	0.0156
			Ciclopirox olamine	0.25	0.25
			Griseofulvin	32	32
			Luliconazole	0.0312	0.0625
		Terbinafine	1	32	
		Singh <i>et al.</i> ^[21] 2018 <i>T. interdigitale</i>	Itraconazole	0.5	2
			Voriconazole	0.25	2
			Fluconazole	32	64
			Luliconazole	0.015	0.06
			Sertaconazole	2	16
			Miconazole	2	8
			Ketoconazole	1	32
			Clotrimazole	4	4
			Amphotericin B	0.5	1
			Griseofulvin	4	8

gloomy antifungal susceptibility pattern, to have multiple topical itraconazole formulations including one that also contains a superpotent corticosteroid and two antibacterial agents is a very dangerous development.^[23] Itraconazole is deemed to be a highly effective antifungal drug for dermatologists in the systemic treatment of recalcitrant dermatophytosis and deep mycosis and for internists in managing various invasive/systemic fungal infections. This drug should never be formulated as a topical formulation as a single molecule or an FDC as that may lead to the rapid development of itraconazole resistance as has been the case with several other antifungal drugs.



Figure 4: Itraconazole (a) soap (b) shampoo and (c) talcum powder

Interestingly, we were unable to find any published paper in an indexed journal on the use of topical itraconazole in dermatophyte infections of the skin. The only published clinical studies of topical itraconazole use on the skin refer to its activity as a hedgehog signaling pathway inhibitor in the treatment/prophylaxis of basal cell carcinoma in mice^[24] and humans.^[25] Even in these studies, it failed to reach high enough concentrations in the epidermal tumors to have a clinical effect on human skin.^[25] Besides, the aqueous solubility of itraconazole is known to be extremely low and the maximally soluble formulation that could be prepared in clinical trials so far was 0.7%. Therefore, to dissolve the drug in topical formulations such as cream or gel at a concentration of 1% is questionable in the absence of a novel drug delivery system, which is not apparent in the products currently available in the market.^[26] Assuming that a suitable formulation is found, it would need to pass through the rigors of safety and efficacy studies mandatory for a new drug which have not been done in these topical formulations and are hence illegal. It would not be remiss to note here that topical itraconazole has been patented by a group of researchers in 2012 itself in the USA^[27] and Europe,^[28] and due consideration should be given to this fact before any permission to manufacture and market it is granted in India.

This discussion is also to reiterate the fact that no responsible regulatory authority in the country should issue a license to manufacture and market such irrational and disastrous formulations. Recently, IADVLT alerted by functionaries of its steroid abuse task force ITATSA, was successful in strongly objecting to such an FDC manufactured by an Indian pharmaceutical company leading to an assurance from the spokesperson of the company to withdraw the product. This seems to be an opportune moment for dermatologists, microbiologists, and the medical fraternity, in general, to approach the Health Ministry officials and sensitize them to the importance of saving itraconazole from such heinous abuse. This molecule is currently the only hope for patients of chronic recalcitrant dermatophytosis [Table 1]. Drug companies jeopardizing its efficacy by illegal manufacturing of itraconazole topical formulations by obtaining invalid permissions from state drug regulators should be strongly discouraged and strong punitive action should be taken against them as well as the state regulators. This level of chaos, insensitivity, and lackadaisical attitude of the concerned authorities in curbing this menace would assuredly tarnish the image of modern India as the country continues its long strides in marching into global limelight in the area of healthcare.

Note: Sales figures have been accessed in June 2020 through a corporate subscription to IQVIA, a global human science data analytics organization that requires an official subscription to access information.

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Conflicts of interest

There are no conflicts of interest.

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