Letters in Response to Previously Published Articles

Isotretinoin may affect pharmacokinetics of itraconazole in the skin: Is it rational to combine both for the treatment of dermatophytosis?

Sir,

This is in reference to the therapy letter, "Successful treatment of recurrent dermatophytosis with isotretinoin and itraconazole" published in your esteemed journal.[1] We read this article with great interest and would like to consider retinoids as another armamentarium to deal with the current menace of dermatophytosis. We do agree with the role of isotretinoin in dermatophytosis as an individual agent, based on its properties as suggested by the authors such as keratolytic effect (resulting in elimination of dermatophytes), increase in skin pH and boosting of humoral and cellular immunity. However, there are some points that need to be explored further to assess the efficacy of itraconazole and isotretinoin combination based on the pharmacokinetic properties of itraconazole.

After oral administration, itraconazole is delivered to the epidermis through passive uptake by keratinocytes in the basal layer and by secretion into sebum and sweat.[2] Tissue levels of itraconazole are 3–20-fold higher than plasma concentration and it persists in the stratum corneum for 3 weeks after stopping therapy, thereby demonstrating a 'reservoir effect' which prevents recurrence of dermatophytosis.[3-5] The drug is eliminated from the body along with shedding of the stratum corneum during the process of epidermal turnover. Since isotretinoin affects epidermal cell kinetics and increases cell turnover, it is likely that coadministration of isotretinoin and itraconazole would result in a rapid clearance of itraconazole from the skin. In this way, isotretinoin can lead to decreased reservoir effect. A similar effect is expected in nails too as retinoids promote nail growth.

Second, itraconazole is a highly lipophilic drug, thus it achieves high levels in sebum.[2] This is in contrast to other azole antifungals such as ketoconazole (which is secreted predominantly in sweat). Sebum levels of itraconazole are five to ten times higher than the corresponding plasma levels while secretion in sweat does not play a major role in delivery of itraconazole to the stratum corneum.[6] Clinically, it results in need of higher doses required for the treatment of palmar and plantar dermatophytic infections, due to the absence of sebaceous glands at these sites.[5] Again, since isotretinoin decreases sebum production considerably, it can lead to decreased therapeutic efficacy of itraconazole.

Furthermore, as it is reported in this particular case, we would also like to comment that initially both oral as well as topical antifungal drugs were given for 2 weeks only and then the drugs were changed. This could have resulted in inadequate duration of therapy, thereby resulting in relapse of lesions and poor response to therapy.

Therefore, we would like to suggest that adequate studies focusing on the effect of isotretinoin on pharmacokinetics of itraconazole, i.e., difference in the level of drug persisting in the stratum corneum and sebum with and without combining isotretinoin should be carried out to further substantiate the role of adding oral retinoids to antifungal therapy.

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Conflicts of interest

There are no conflicts of interest.

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