Rational for Drug Dosimetry and Duration of Terbinafine in the Context of Recalcitrant Dermatophytosis: Is 500 mg Better than 250 mg OD or BD?

Kabir Sardana, Aastha Gupta

From the Department of Dermatology, Dr. Ram Manohar Lohia Hospital, New Delhi, India.
E-mail: kabirjdv@gmail.com

Indian J Dermatol 2017;62(6):665-7

Sir,

We read with interest the study by Babu et al.,[1] where 500 mg of terbinafine was used in apparently recalcitrant dermatophytosis and although there are multiple causes for this recalcitrance including steroid abuse, drug updosings is not a likely solution and we would like to highlight the pharmacological incongruities of this approach.[2]

Drug dosimetry is dependent on three steps before their clinical utility can be assessed.[3] The most basic involves the experimental determination of the pharmacokinetic/pharmacodynamics (PK/PD) levels of the drug. This is followed by assessing the drug’s skin PK/PD index and then assessing the proper dose and understanding the level of treatment efficacy desired. This is followed by its clinical application.

Pharmacokinetic/Pharmacodynamics of Terbinafine and its Dosing

The ideal PK/PD measure (index) which is most closely related to efficacy depends on parameters linking the drug PK, minimal inhibitory concentration (MIC), and drug effect. These include peak drug concentrations in relation to the MIC (Cmax/MIC), the area under the drug concentration curve in relation to MIC (area under the curve/MIC), and the time (expressed as a percentage of the dosing interval) that drug concentrations are expected to exceed the MIC (%T > MIC). Drugs that are concentration dependent like terbinafine use, %T > MIC as the cardinal parameter, which essentially means that a multidosing strategy is a better predictor of clinical response, thus, a twice a day dose is better than increasing the single dose as reported in this study.[4] Hence, if there is a compelling reason to updose, 250 mg BD is a more rational dose than 500 mg OD. In fact, a study has confirmed that for Trichophyton mentagrophytes with a MIC value of 0.01 µg/mL and a T > MIC (h) of 17.6 h, a twice-daily dosing is ideal.[5] Human volunteer trials Jensen et al., 1990, Schatz et al., 1987, and Stephen et al., 1987 have found a T ½ ranging from 11.35 to 16.4 h, which also makes a BD dose pharmacologically logical.[6]

Clinical Application and Skin Pharmacokinetic Levels

It must be understood that the serum levels of terbinafine with a dose of 250 mg follow the predictive PK/PD, but the plasma levels do not parallel the levels at the site of action that is the skin. Faergemann et al. determined terbinafine levels in serum, stratum corneum, dermis–epidermis (without stratum corneum), hair, sebum and eccrine sweat before, during, and after 250 mg doses orally to volunteers once daily and found that terbinafine is concentrated rapidly in stratum corneum (up to 9.1 µg/g of tissue) primarily by diffusion from the vascular system through the dermis–epidermis. It also reached a high concentration in sebum (up to 45.1 µg/ml) but was not found in the sweat. The plasma levels were markedly lower at 0.1-1.0 µg/ml. Furthermore, the level in the skin was about 10-40X than the MIC of the fungi.[7] Another study done by Faergemann et al. evaluated the skin levels after 250 mg orally once daily for 7 and 14 days. In the 7-day study, high terbinafine levels were found in sebum (19 µg/g) and stratum corneum (2-5 µg/g) and in the stratum corneum, a concentration above the minimal inhibitory concentration for most dermatophytes was still found 48 days after the last day of medication. Moreover, even 54 days after stopping treatment, it was 100-1000 times higher than the MIC for most dermatophytes.[8]

Another study used a lower dose of terbinafine at 125 mg OD and found that the concentration in the stratum corneum in hyperkeratotic type tinea pedis cases, was 247.80 ng/g, which was approximately 50 times higher than the MIC (3–5 ng/ml) at 1-week posttreatment, and was still higher than the MIC, at 50.73 ng/g, 6-week posttreatment.[8] Hence, at conventional doses (125–250 mg), the drug is not only secreted preferentially through the sebum-to-lipid rich sites but also achieves higher levels than the serum. Thus, with conventional doses, MIC levels are thus, there is little rationale for a higher dose as seen in this study.[1]

Methodological and Analytical Issue

This study is not a prospective controlled clinical trial which can assess efficacy and safety of terbinafine dose 500 mg. Moreover, the study did not use the standard regimen that is terbinafine 250 mg once a day arm or for that matter 250 mg BD dose to compare the results with 500 mg dose.

Glaringly, the authors referred to studies by Arca et al. and Farag et al., who used terbinafine 250 mg once a day...
and Cole and Stricklin and Hay et al., who used 250 mg twice a day regimen, all of which align with the above theory of conventional dosage.[10-13] Most importantly the studies where 500 mg terbinafine doses have been compared with other drugs and quoted as a defense by the authors, are actually 250 mg BD doses, which has been misconstrued as a single dose of 500 mg.[12,14] Authors have referred to Dolton study to justify the use of terbinafine high dose in the management of dermatophytosis. However, the article discusses the role of high-dose terbinafine to treat cutaneous and subcutaneous mycoses, such as sporotrichosis, eumycetoma, and chromoblastomycosis, as well as in combination with other antifungal agents to treat resistant or refractory invasive fungal infections such as Aspergillus spp., zygomycetes, Fusarium spp., Paecilomyces spp., Candida albicans, dematiaceous molds, and the highly resistant Scedosporium prolificans. Hence, findings from the article may not be relevant to manage recalcitrant dermatophytic superficial skin infections where the target skin concentration plays an important role rather than plasma concentration.[15]

Baseline and follow-up liver function tests were not performed in all patients. While only a few reports exist for side effects caused by 500 mg dose, ocular side effects have been observed with terbinafine 500 mg/day use. Bilateral anterior optic neuropathy with decreased vision and optic disc edema was reported in a patient 2 weeks after starting terbinafine (500 mg/day).[16,17] Even conventional doses can cause hepatic side effects and giving high doses (500 mg) is not justified.[18]

**Conclusion**

Thus, it must be emphasized that terbinafine, even at conventional doses achieves skin levels that exceed trough plasma levels by a factor of 75, well above the MICs for dermatophytes. A higher dose if warranted should be in a divided dose (250 mg BD) than a single dose of 500 mg, which defies the basic principles of PK/PD of the drug. By extension, it reflects unfavorably on the argument of resistance as the levels achieved by terbinafine are sufficiently higher than the MIC, hence probably the answer lies in the suppressed immune response possibly due to steroid abuse.[2]

It must be pointed out that there is no rationale of mg/kg weight dosing (used in animal models) as even at conventional doses the levels achieved in the skin surpass the MIC of the fungi. Furthermore, the apparent rigidity of duration to 2–4 weeks is not necessary as exemplified by Villars and Jones in their article, who said the duration of treatment was based on the accepted practices and experience in the therapy of the various dermatomycoses, and is, 3–6 weeks for tinea corporis/cruris and 6 weeks for tinea pedis.[14]

Notwithstanding the above arguments, if it is shown that the minimum fungicidal concentration of the prevalent species in India is higher than the skin levels achieved by terbinafine 250 mg, then possibly an updosing may be justified, that too in a divided dose of 250 mg BD. But, there is definitely no rationale for a 500 mg single dose in superficial fungal infection like dermatophytosis.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Babu PR, Pravin AJS, Deshmukh G, Dhoot D, Samant A, Kotak B, et al. Efficacy and safety of terbinafine 500 mg once daily in patients with dermatophytosis. Indian J Dermatol 2017;62:395-9.
2. Sardana K, Mahajan K, Arora P, editors. Recalcitrant dermatomycosis: Focus on tineacorporis/cruris/pedis. In: Fungal Infections: Diagnosis and Management. Delhi: CBS; 2017. p. 23-39.
3. Andes D. Clinical utility of antifungal pharmacokinetics and pharmacodynamics. Curr Opin Infect Dis 2004;17:533-40.
4. Sakai MR, May ER, Imernan PM, Felz C, Day TA, Carlson SA, et al. Terbinafine pharmacokinetics after single dose oral administration in the dog. Vet Dermatol 2011;22:528-34.
5. Kotnik T, Erzen NK, Kuzner J, Terbina A, Carlson SA, Noxon J0, et al. Terbinafine pharmacokinetics after single dose oral administration in the dog. Vet Dermatol 2011;22:528-34.
6. Jensen JC. Clinical pharmacokinetics of terbinafine (Lamisil). Clin Exp Dermatol 1989;14:110-3.
7. Faergemann J, Zehender H, Jones T, Maibaech I. Terbinafine levels in serum, stratum corneum, dermis-epidermis (without stratum corneum), hair, sebum and eccrine sweat. Acta Derm Venereol 1991;71:322-6.
8. Faergemann J, Zehender H, Millerioux L. Levels of terbinafine in plasma, stratum corneum, dermis-epidermis (without stratum corneum), sebum, hair and nails during and after 250 mg terbinafine orally once daily for 7 and 14 days. Clin Exp Dermatol 1994;19:121-6.
9. Kikuchi I, Tanuma H, Morimoto K, Kawana S. Usefulness and pharmacokinetic study of oral terbinafine for hyperkeratotic type tinea pedis. Mycoses 2008;51:7-13.
10. Mishra M, Panda P, Tripathy S, Sengupta S, Mishra K. An open randomized comparative study of oral itraconazole pulse and terbinafine pulse in the treatment of onychomycosis. Indian J Dermatol Venereol Leprol 2005;71:262-6.
11. Farag A, Taha M, Halim S. One-week therapy with oral terbinafine in cases of tinea cruris/cruris. Br J Dermatol 1994;131:684-6.
12. Cole GW, Stricklin G. A comparison of a new oral antifungal, terbinafine, with griseofulvin as therapy for tinea corporis. Arch Dermatol 1989;125:1537-9.
13. Hay RJ, Logan RA, Moore MK, Midgely G, Clayton YM. A comparative study of terbinafine versus griseofulvin in ‘dry-type’ dermatophyte infections. J Am Acad Dermatol 1991;24:243-6.
14. Villars V, Jones TC. Present status of the efficacy and tolerability of terbinafine (Lamisil) used systemically in the
The pharmacodynamic parameter that is most often given below.

Sir,

We have conducted this survey in patients with recalcitrant dermatophytosis. Kindly find the detailed explanation of the same as context of recalcitrant dermatophytosis.

Dr. Gaurav Deshmukh
Glenmark Pharmaceuticals, Mumbai, Maharashtra, India.

From the Consultant Dermatologist, Raga Skin Care, Bengaluru, Karnataka, India.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Access this article online

Quick Response Code: [QR Code Image]
Website: www.e-ijd.org
DOI: 10.4103/ijd.UJ_435_17

How to cite this article: Sardana K, Gupta A. Rational for drug dosimetry and duration of terbinafine in the context of recalcitrant dermatophytosis: Is 500 mg better than 250 mg OD or BD? Indian J Dermatol 2017;62:665-7.

Received: September, 2017. Accepted: September, 2017.