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Fluconazole induced herpes labialis-like lesions in an adult male

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CASE STUDY

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Abstract

Fluconazole is a bistriazole commonly prescribed for the treatment of various fungal infections caused by yeasts and dermatophytes. However, there have been several reports of rare Adverse Drug Reactions (ADRs) like Fixed Dose Eruption (FDE), Toxic Epidermal Necrolysis and Stevens Johnson Syndrome following oral administration of fluconazole. We report a rare case of fluconazole induced oral mucosal lesions, mimicking herpes labialis, in a 34 year old male patient receiving oral fluconazole for the treatment of allergic fungal sinusitis.

Case report

A 34 year old man presented with multiple, painless, shallow erosions, measuring about 1 cm in diameter, over the mucosal surface of the upper lip and the outer surface of the lower lip along with burning, itching and crusting. The erosions developed from painful vesicles characteristic of localised herpes simplex. Tzanck test for herpes simplex infection was negative. The patient suffered from perennial allergic rhinosinusitis for one year which was treated with topical steroids, antibiotics and antihistaminics leading to intermittent remission of symptoms. A CT scan of the paranasal sinuses showed opacification of both the maxillary and anterior ethmoid sinuses with diffuse intrasinus area of increased attenuation, suggesting fungal sinusitis. Hence, oral fluconazole 150mg once daily was started presumptively for a week. History revealed that fluconazole treatment was concomitantly associated with the development of herpes labialis-like vesicles. The first episode of blistering started after the intake of the third tablet of fluconazole. There were no other constitutive symptoms. Therefore, a Fixed Dose Eruption (FDE) to fluconazole was suspected. Oral provocation test with fluconazole 150mg was performed in the following week with the patient's consent. The patient developed burning sensation and erythema on the mucosal aspect of both the lips, developing into herpes-like vesicles at the same site on the very next day and painful erosions by the fourth day, mimicking the earlier episode. (Figure 1)The erosions healed within a week of stopping fluconazole and the patient continued receiving treatment for allergic rhinosinusitis. The ADR was reported to the peripheral pharmacovigilance centre of the state under the National Pharmacovigilance Programme India.

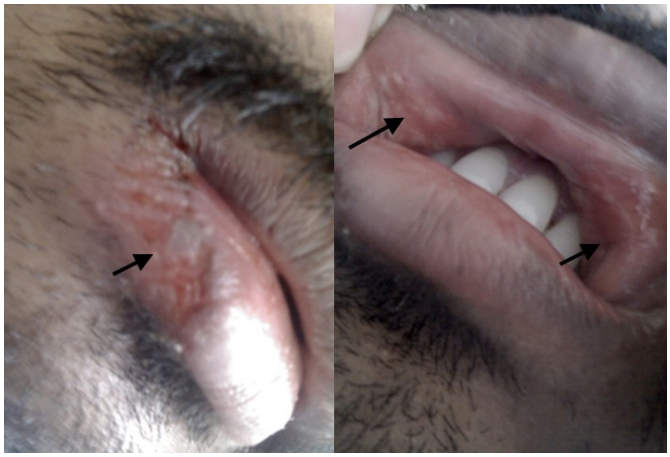

Figure 1. Pre and post provocative (left and right respectively) fluconazole induced lip lesions.

Discussion

Brocq in 1894 was the first to introduce the term FDE, although the phenomenon was described by Bourns 5 years earlier.[1] FDEs usually occur as a solitary pruritic, erythematous macule which evolves into an oedematous plaque. Vesicles and bullae with a prominent hemorrhagic component may be present in the later stages.[2] Bullous FDEs mimicking herpes simplex virus infection too has been described in the past.[3]

FDE is characterized by single or multiple skin lesions that occur at the same site each time a drug is administered. However, the number and size of sites may increase after each exposure. Lesions are usually round or oval and well defined. Swelling and redness of skin are typically seen within 30 minutes to eight hours after exposure. The exact mechanism underlying FDEs is not known but immunological studies strongly indicate a role of the immune system. The drug may act as a hapten and bind to the protein component in melanocytes or dyskeratotic keratinocytes forming a drug-protein complex which is then detected, processed and presented to lymphocytes in the dermis or regional lymph nodes by Langhans' cells as seen in allergic contact dermatitis. There is subsequent activation of B and T lymphocytes producing lymphokines and antibodies which cause inflammation and damage to cells in the basal layer.

The most common drug causing FDEs is cotrimoxazole (sulfamthoxazole/trimethoprim), others include tetracycline, metamizole, phenylbutazone, paracetamol,

acetyl salicylic acid, mefenamic acid, metronidazole, tinidazole, chlormezanone, amoxicillin, ampicillin, erythromycin, griseofulvin, phenobarbitone, diclofenac, indomethacin, ibuprofen, diflunisal, pyrantel pamoate, clindamycin, allopurinol, and albendazole.[4]

The first case of fluconazole induced FDE was reported in year 1994 by Morgan and Carmichael, where they described the reaction in a 27 year old man with an 18 month history of 15 episodes of recurrent rash on the extensor surfaces of his elbows.[5] In the second case, a local provocation with 10% fluconazole test in petrolatum applied at the site of a previous lesion of FDE reproduced the eruption clinically and histopathologically in a 36 year old woman.[6] Subsequently few more case reports implicated the causation of FDEs with fluconazole from limited skin involvement to extensive generalized lesions.[7,8,9,10] The most affected sites for eruptions were limbs, palmar and plantar areas as well as the oral cavity and lips.[11] A report of palatal FDE due to fluconazole has also been published in the past.[12]

Most previous studies on FDE due to drugs demonstrated a higher occurrence in men compared to women[4] that is in congruence with our finding as well. However, majority of the FDEs due to fluconazole occurred in women as compared to men.[11] Only one case of fluconazole induced recurrent vesicles on the lower lip, mimicking herpes simplex virus infection, in a 23 year old woman, has been reported so far. [13] In this case the lesions developed after 6 months of recurrent fluconazole intake for Chronic Recurrent Vulvovaginal Candidiasis (CRVC). Oral provocation test with increasing doses of fluconazole in the above patient produced herpes like vesicles within one day, at the same site. Other antifungals implicated in causing FDEs are terbinafine[14], griseofulvin[15], ketokonazole[16], itraconazole[17] and nystatin.[18]

Fluconazole is generally well tolerated but the possibility of it causing sensitization and allergic reactions should be born in mind, especially in case of long term therapy in patients with recurrent infections. Any new, localised skin lesion, during the course of such therapy, should be considered potentially drug induced unless proved otherwise.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.