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Fluconazole and fixed drug eruption

Introduction

Fluconazole (Diflucan®) is a triazole antifungal agent. The mechanism of action of fluconazole is similar to that of other imidazole and triazole antifungal agents, specifically, inhibition of fungal cytochrome P-450-dependent ergosterol synthesis and thereby inhibition of cell membrane formation. It appears to have a greater selectivity for fungal as compared to human P-450-enzymes.
It was approved for the Dutch Market in 1990 for the following indications: *Vaginal candidiasis, (prophylaxis of) oropharyngeal candidiasis, esophageal candidiasis, deep systemic candidiasis, cryptococcal meningitis and as maintenance treatment in patients with AIDS as prevention of a relapse of cryptococcal meningitis* [1]. Fluconazole has a long half life, which permits once daily dosing. In vaginal candidiasis single doses of 150 mg have been effective.
Commonly observed adverse events are nausea, vomiting and elevations in liver function tests. Observed hypersensitivity reactions are anaphylactic reactions, angioedema and facial oedema, pruritus, urticaria, erythemateous –or maculopapular rash and exfoliative skin reactions, including Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)[1,2].

Reports

Lareb received five reports of fixed drug eruption (FDE) on fluconazole capsules between 1996 and 2002 from various healthcare professionals. Fixed drug eruption is a sharply demarcated erythema, oval or circular in shape, which recurs in exactly the same place after following exposure to a specific drug. Usually there is only one lesion, but two or more may be present. The size varies from a few millimetres to 10-20 cm in diameter. Initially it is a dusky red lesion with oedema, followed by development of vesiculae or bullae. Healing takes place with pigmentation. The FDE may be localized on skin and mucous membranes.
The first report concerned a 20-year-old woman, known with manifestations of herpes simplex and nickel allergy. She had used fluconazole 200 mg capsules once monthly for vaginal candidiasis for 2 years, when the first episode of FDE appeared. On the day of exposure she experienced redness and swelling on the left side of the lower lip. Afterwards the lesion became pigmented. Each month, after intake of a tablet fluconazole, the lesion recurred. As co medication she used ethinylestradiol/cyproteronacetate. Eight months later fluconazole was discontinued. A post-inflammation hyperpigmentation remained.
Lareb received four other reports of FDE in association with use of fluconazole. Twice the inner part of the hand was affected, with formation of blisters. Another report showed a sharp circumscribed flaming red swelling on the right side of the tongue within hours after intake of fluconazole 50 mg. In the last case symptoms existed of redness, itching and vesicles on the right forearm, which occurred four times after intake of fluconazole 150 mg in a 31-year-old woman. Biopsy revealed a superficial and deep perivascular and interstitial inflammation with many leucocytes and violation of the epidermis/dermis boundary. After discontinuation of fluconazole this patient recovered.

Other sources of information

Literature.

Three publications of fixed drug eruption have been published [3,4,5]. In the first publication a 27-year-old man suffered from 15 episodes of FDE on the extensor surfaces of his elbows, each lasting three days and resolving spontaneously to leave residual bluish-gray macules. Biopsy showed spongiosis, hydropic degeneration of the basal layer, a predominantly lymphocytic perivascular infiltrate and dermal melanophages. Each time he had used fluconazole 150 mg for candidal balanitis within hours before symptoms appeared [3]. In another case a local provocation test with 10 % fluconazole in petrolatum applied at the previous lesion of FDE reproduced the eruption clinically and histopathologically [4].

Databases

The WHO combinations database contains 17 reports of FDE disproportionally associated with the use of fluconazole (Odds ratio 4.55, 95% CI 2.82 – 7.33).

Mechanism

The pathogenic mechanism is unknown. In FDE vesiculae or bullae may follow the initial lesion. A re-administration of the suspected drug may result in extensive bullous lesions, which is occasionally so extensive as to mimic TEN [6].

Conclusion

Lareb has received five reports of fixed drug eruption on fluconazole. The association between fixed drug eruption and fluconazole is supported by the publications in the literature and findings in the WHO database.

References

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