Fluconazole and Fixed Drug Eruption

Introduction

Fluconazole is a triazole antifungal agent. It is indicated *for the treatment of oropharyngeal and vaginal Candida infections*, but also for the *treatment of deep systemic Candida infections*. Further indications are the *prophylaxis of (oropharyngeal) Candida in patients with AIDS or with neutropenia, caused by radiation, chemotherapy or bone marrow transplantation*. Fluconazole is also used as *treatment of crytococcus meningitis and as prophylaxis of Cryptococcus meningitis in patients with AIDS*. It was approved for the Dutch market in 1990 [1].

A Fixed Drug Eruption (FDE) is a sharply demarcated erythema, oval or circular in shape, which recurs in exactly the same place following exposure to a specific drug. Usually there is one lesion, but two or more may be present. The size varies from a few millimeters to 10-20 cm in diameter. Initially it is a lesion of dusky erythema and edema, sometimes followed by development of vesiculae or bullae. The lesions may itch, but burning sensations are also common. Healing takes place with pigmentation in most cases. The FDE may be localized on skin and mucous membranes. Drugs most frequently implicated are antibiotics, antifungals, NSAIDS, ACE inhibitors, calcium channel blockers, proton pump inhibitors and psychotropic drugs [2].
The Dutch SPC of fluconazole mentions the following skin reactions as adverse reactions: rash, pruritus, urticaria, alopecia, angioedema, face edema and exfoliative skin reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis(TEN) [1].

Reports

Until the 1st of May 2007 Lareb received 6 reports of FDE in association with fluconazole. All reports were in women; the indication for fluconazole was vaginal mycosis/candidiasis in five patients, in one patient the indication was unknown. Twice the inner part of the hand was affected, once the right forearm, once the plantar side of the foot, once the lip and once the tongue (patient B). In all patients the eruption occurred after each intake of fluconazole, with a range between two and eight times after administration.
A biopsy was taken in patients B and D. In patient B it mimicked a lichen ruber planus, but with major ulceration. After further consultation the diagnosis of fixed drug eruption was confirmed. In patient D superficial and deep perivascular and interstitial inflammation with disturbance of the boundaries was observed with presence of leucocytoplasia, as in vasculitis. Beside this many plasma cells were shown. Blood- and urinary samples in this patient showed no abnormalities.
The medical history of patient E included herpes simplex infections, but she had not suffered from these for 2-3 years. Furthermore she was known with nickel allergy. Patient had been using fluconazole once monthly for 2 years before the first reaction developed. Because in first instance an allergy was suspected in this patient, standard contact allergy investigations were performed, which revealed no allergic reactions after 72 hours. The active lesion of the lip resolved each time within two days, leaving a hyperpigmented spot. The patient was treated with triamcinolon cream for 3 months, but hyperpigmentation on the lip remained.

Table 1. reports of Fixed Drug Eruption associated with the use of fluconazole

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A F, 44	fluconazole 150 mg monthly vaginal mycosis	propranolol, sumatriptan, hydrochlorothiazide	bullous eruption palmar side left hand > 1 cm occurred three times	2 hours not reported
B F, 25	fluconazole 50 mg once daily vaginal candidiasis	not reported	red ,sharply demarcated eruption right side tongue same reaction after 3 months	8 hours recovered
C F, 37	fluconazole 150 mg once daily vaginal candidiasis	not reported	bullous eruption palmar side hands same reaction 2 years before	hours not recovered after 3 days
D F, 31	fluconazole 150 mg once daily not reported	Ibuprofen IUD with levonorgestrel	redness, vesicles, pruritus on right forearm, four times in total	not reported not known
E F, 20	fluconazole 200 mg monthly vaginal candidiasis	ethinylestradiol/ cyproteron naproxen if needed	swelling, itching left side lower lip (monthly, during 8 months)	hours recovered with sequelae (hyperpigment ation)
F F, 43	fluconazole 150 mg once daily vaginal candidiasis	not reported	painful bullous eruption plantar side foot, twice	1 day recovering after 1 day

Other sources of information

Literature

Several articles upon fixed drug eruption in association with fluconazole have been published [3-8].
Morgan described a 27 year old male, who suffered during a period of 1.5 years from 15 episodes of rash on the extensor surfaces of his elbows, lasting for three days, leaving residual bluish-grey macules. Biopsy showed appearances consistent with a fixed drug eruption. The medical history disclosed intake of fluconazole 22 times over the previous three years as a single dose treatment for candidal balanitis. Rechallenge with fluconazol provoked identical signs within an hour [5].
Heikkila reported upon a 36 year old woman with red maculae on the left thigh and distal phalanx on the right fourth finger, fading in a few days, but with development of a long-lasting violet pigmentation on the thigh. She had been using 18 fluconazole capsules during the previous 44 months. 12 hours after another intake of fluconazole she again developed erythematous patches on the same site. Skin biopsy of the thigh confirmed the diagnosis of FDE [6]

Ghislain published a third case of FDE in a 21 year old woman with dusky erythematous macules on the left temple, the superior lip, the right palm and the great toe of the left foot. The day before the patient had taken her ninth tablet of fluconazole 200 mg for vaginal candidosis. The lesions disappeared within a few days. One month later, after the tenth tablet of fluconazole, lesions reappeared in the same places within a few hours. Patch tests with fluconazole, also on previous sites of FDE was negative, but oral provocation was positive [7].
Lane described a 24 year old woman, who presented with a tender erythematous patch with dusky centre on the mucosal surface of her lower lip, occurring two days after taking a single dose of fluconazole 200 mg. She reported an identical, but less severe reaction, following a course of fluconazole taken several months earlier [4].
Recently Mahendra reported upon development of an erosion of the hard palate, existing since two days, in a 19 year old boy. He had been taken oral fluconazole 150 mg weekly and topical terbinafine cream for extensive tinea corporis and cruris. The symptoms started 7-8 hours after the first dose of fluconazole. On further enquiry the patient recalled history of a similar episode one year ago, one day after he had taken fluconazole; that lesion had been smaller in size and had healed over time without treatment. This time, treatment with chlorhexidine mouth rinse, oral cetirizine and topical triamcinolon was started and healing took 15 days. Oral provocation with fluconazole 50 mg four weeks later resulted in reappearance of the lesion in three hours [8].

Databases

On the 1st of May 2007 the database of the Netherlands Pharmacovigilance Centre Lareb contained 6 reports of Fixed Eruption in association with fluconazole. The reporting odds ratio for this association is 222 with a confidence interval of 83-542. The database of the Uppsala Monitoring Centre of the WHO contained 18 reports of fixed eruption, which is also disproportional (ROR 2.8; 95% CI 1.7-4.4).

Mechanism

The pathogenic mechanism of FDE is not completely elucidated, but the condition is assumed to be caused by a delayed (type IV) allergy. Histologically, lesions show mononuclear infiltrate along the dermo-epidermal junction. Effector memory T cells are homing in the lesion and are probably involved in local skin memory. Patch testing at a not-involved skin area is frequently negative, however patch testing on the affected site might give positive results. A negative outcome does not exclude FDE; oral provocation is warranted to confirm the diagnosis of FDE. This should however be done cautiously as rarely extensive bullous lesions may occur, sometimes mimicking TEN [2,7].
It should be noted that TEN, but also SJS, are both considered to be generalized allergic type IV reactions, in which T lymphocytes probably play an important role [9].

Conclusion

Lareb received 6 reports of fixed drug eruption in association with fluconazole. Mandatory for the diagnosis is the recurrence of the lesion on exactly the same place after renewed exposure of the drug, which was shown in all patients. This

association is supported by a disproportionally number of reports of fixed eruptions on fluconazole in the Lareb as well as in the WHO databases and several publications upon this association in the literature. Therefore, fixed drug eruption should be listed in the SPC of fluconazole.

References

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- Signal concerning fixed drug eruption and fluconazole
- Fixed drug eruption is not listed in the SPC of fluconazole