Fluconazole and fixed drug eruption – an update

Introduction

Fluconazole (Diflucan®, generic) is a triazole antifungal agent. Fluconazole 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 has been 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 after 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. Drug groups most frequently implicated are antibiotics, antifungals, NSAIDS, ACE inhibitors, calcium channel blockers, proton pump inhibitors and psychotropic drugs [2].

The current observation describes the association between fluconazole and fixed drug eruption in 13 patients. A previous report regarding this association in 6 patients was sent to the Medical Evaluation Board (MEB) in 2007 [3].

Reports

From July 25 1996 till October 16, 2014 in total 13 reports of fixed drug eruption associated with the use of fluconazole were sent to the Netherlands Pharmacovigilance Centre Lareb. All patients were women, because fluconazole was indicated for vaginal candidiasis. In all patients the eruption occurred after each subsequent intake of fluconazole, with a range between two and eight recurrences. The reports are listed in Table 1.

Table 1. Reports of fixed drug eruption associated with the use of fluconazole

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 14643 F, 41-50 years Pharmacist	fluconazole 150 mg monthly vaginal mycosis	propranolol, sumatriptan, hydrochlorothiazide	bullous eruption palmar side left hand > 1 cm occurred three times	2 hours discontinued not reported
B 24498 F, 21-30 years Specialist doctor	fluconazole 50 mg once vaginal candidiasis	not reported	red ,sharply demarcated eruption right side tongue same reaction after 3 months	8 hours discontinued recovered
C 27197 F, 31-40 years Pharmacist	fluconazole 150 mg once vaginal candidiasis	not reported	bullous eruption palmar side hands same reaction 2 years before	hours discontinued not recovered after 3 day
D 29967 F, 31-40 years Pharmacist	fluconazole 150 mg once not reported	ibuprofen IUD with levonorgestrel	redness, vesicles, pruritus on right forearm, four times in total	not reported discontinued recovered

E 38107 F, unknown Specialist doctor	fluconazole 200 mg monthly vaginal candidiasis	ethinylestradiol/ cyproteron naproxen if needed	swelling, itching left side lower lip (monthly, during 8 months)	hours discontinued recovered with sequelae (hyperpigmentation
F 64444 F, 41-50 years Pharmacist	fluconazole 150 mg once vaginal candidiasis	not reported	painful bullous eruption plantar side foot, twice	1 day not applicable recovering after 1 day
G 77291 F, 31-49 years Specialist doctor	fluconazole 150 mg monthly vaginal candidiasis	not reported	burning red swelling in face (8 times)	3 month discontinued after 8 months recovered
H 84629 F, 61-70 years Pharmacist	fluconazole 150mg inguinal fungal infection	miconazole/hydro-cortisone cream	fixed drug eruption (unknown times)	11 days unknown recovered
I 87430 F, 41-50 years Specialist doctor	fluconazole 50mg monthly vaginal candidiasis	not reported	fixed drug eruption face (same reaction before)	14 years discontinued recovered
J 90332 F, 41-50 years General Practitioner	fluconazole 150mg vaginal candidiasis	not reported	fixed drug eruption (in total 4 times)	hours discontinued recovered
K 138647 F, 31-40 years Pharmacist	fluconazole 150mg vaginal mycosis	insulin lispro	fixed drug eruption lip (two times)	30 minute not applicable recovering
L 147747 F, 41-50 years Consumer	fluconazole 150 mg mycosis	not reported	fixed drug eruption (toes, several times)	s48 hour discontinued recovered
M 168905 F, 31-40 years Pharmacist	fluconazole 150 mg fungal infection amoxicilline unknown indication		fixed eruption on the lip(3 times)	30 minute amoxicillin: no change unknown outcome fluconazole: not applicable unknown outcome

A biopsy was taken in patient 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 interfaces was observed with presence of leucocytoclasia, 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 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 triamcinolone cream for 3 months, but hyperpigmentation on the lip remained.
In case J, the reporting general practitioner is also the patient. She experienced also a FDE on partly swallowed miconazole oral gel, but the reaction was less severe. Patient L experienced an inflammation in her toes of the left foot each time after intake of fluconazole in the pill- free week. The one time she did not use fluconazole, she experienced no reaction.

Patient M experienced a FDE on the lip three times after using both amoxicillin and fluconazole. Amoxicillin was continued, fluconazole was only administered once at the time. Patient was treated with acyclovir or zinc-sulphate. Outcome is not known.

Other sources of information

SmPC

The Dutch SmPC of fluconazole mentions the following skin reactions as adverse reactions: rash, drug eruption, pruritus, urticaria, perspiration, alopecia, angioedema, face edema, Acute Generalised Exanthematous Pustulosis (AGEP) and exfoliative skin reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis(TEN) [1]. Although drug eruption is included, Fixed Drug Eruption, which is a specific diagnosis, is not described.

Literature

Case reports of fixed drug eruption have been described in association with fluconazole [4-16]. The Netherlands Pharmacovigilance Centre Lareb has paid attention to this association in 2009 [17]. Details of literature case reports dated 2007 or before, can be found in the previous observation sent to the MEB [3]. The more recent publications are described underneath to show the various expressions of FDE on different parts of the body.

A 23-year-old woman presented with recurrent herpetiform vesicles of the lower lip, but all diagnostic measures for herpes virus infection including herpes viridae specific PCR were negative. Medical history revealed that she also had chronic recurrent vulvovaginal candidiasis, which had been treated with various regimes, including repetitive applications of fluconazole. Consequently, fluconazole-induced fixed drug eruption was suspected, but skin tests performed with fluconazole remained with-out response. It is known that skin patch testing at a not-involved skin area is frequently negative and does not exclude FDE (patch testing on the affected site might give positive results). Consecutive repeated oral provocation tests with fluconazole were carried out and resulted in the development of burning herpetiform vesicles of the lower lip. Histopathology revealed a subepidermal and superficial perivascular infiltrate, basal vacuolated and apoptotic keratinocytes, intra-epidermal lymphocytes and intra-epidermal multilocular vesicles. Together with the clinical history and picture, fluconazole-induced fixed drug eruption mimicking labial herpes simplex virus infection was diagnosed. Oral provocation tests with an alternative systemic antifungal treatment, itraconazole, were well tolerated, systemic therapy with itraconazole was initiated, and no further labial vesicles developed [8].

A 35-year old woman experienced three periods of a painful vulva blister, accompanied by a solitary, well-demarcated, 15 cm diameter, erythematous patch with central vesicles on the left chest wall; the last two times also oral ulceration was observed. Empirically treatment with aciclovir or valciclovir ws initiated, leaving post inflammatory hyperpigmentation. Bacterial, viral and fungal swabs taken on each occasion were negative [9].

Jensen reported upon a 38-year old woman, with peculiar prickly nummular oedematous dusky red skin lesions on her thighs, left popliteal fossa and lips, accompanying labial candidiasis, for which she used fluconazole. She also used interferon for multiple sclerosis and occasionally dexibuprofen due to flu-like symptoms. Patch tests with dexibuprofen and fluconazole, also on hyperpigmented areas, were negative. Oral provocation with dexibuprofen was also negative, but with fluconazole was positive within hours [10].

Pai described a 33-year-old male with a history of rash associated with burning and itching, 5 hours after intake of fluconazole 150 mg for tinea cruris. There was a history of similar lesions in the past due to some medication for a similar dermatological complaint. On examination, well-defined erythematous plaques of varied sizes were present over the chest (10x 10 cm), back, lower limbs, and lips. A patch test done with the offending drug was positive. After discontinuation of fluconazole and treatment with oral antihistamines and topical steroids, he recovered within five days [11]

A 24-year-old woman presented with a recurrent, raised, red rash consisting

of lesions, one to two centimetres in diameter, on the backs of both hands. The patient reported that the plaques, became blisters and faded to circular violet patches, healing within one week with residual hyperpigmentation. The patient reported nine similar episodes in the same location, and two such episodes on her face. The eruptions occurred after self-administered oral fluconazole for vaginal candidiasis. After discontinuation of this medication, no recurrences occurred. She had no reaction to the subsequent use of topical clotrimazole [12].
A 34-year-old woman experienced a slight pigmented macule on the right elbow and faint erythema with scale on the left elbow since 9 days. With time, the macules faded and pigmentation developed. She described two similar episodes in the same location that had occurred about 1 year and about 5 months ago, respectively. Histopathological findings were consistent with FDE. She used naproxen regularly to reduce pain during menstruation. Fluconazole had been used irregular during the last 3 years and the three episodes of eruption corresponded with the time of fluconazole intake [13].
Lester reported upon a 30-year old woman with AIDS, who had a mild bullous cutaneous reaction after using fluconazole for oral thrush, which left a residual hyperpigmentation. Three months later, within hours after a single dose of fluconazole, she developed burning and erythema of the extremities, which progressed to non-pruritic patches, macules and eventually blisters and bullae involving the trunk, face extremities, mostly in the already hyperpigmented areas, accompanied by fever, tachycardia and hypotension. There was no involvement of oral mucosae, conjunctiva, palms or soles. This absence and the involved hyperpigmented areas, timing and rapid resolution with corticosteroids pointed into a direction of widespread bullous FDE, although an overlap in clinical presentation with TEN was demonstrated [15].
A 64-year-old woman presented with eight ovoid hyperpigmented patches on the arms, palm and lower leg that had recurred multiple times at the identical sites at seemingly random intervals over the prior six months. The clinicopathologic diagnosis strongly favored FDE, though the culprit medication remained elusive. Further evaluation and oral re-challenge confirmed the diagnosis of FDE to fluconazole [14].

Cross sensitivity
A few publications suggest a possible cross sensitivity between fluconazole and itraconazole or fluconazole and ornidazole [18,19].
A 52-year-old female was administered a single 400 mg dose of fluconazole for extensive pityriasis versicolor. Within 12 hours, she noticed 3 oval, painful, eroded, pigmented patches over her trunk with diameters of 3 cm to 4 cm and erythematous halos. A clinical diagnosis of FDE caused by fluconazole was made. An oral graded challenge with fluconazole, itraconazole, and ketoconazole was performed at 4 weeks. Reactivation was observed with fluconazole (25 mg) and itraconazole (25 mg) orally within 12 hours, but ketoconazole (in 50, 100, and 200 mg doses) failed to reactivate the lesions. This confirmed a FDE to fluconazole with a cross sensitivity to itraconazole but not to ketoconazole. Fluconazole, itraconazole, and ketoconazole have a marked structural resemblance, because they all belong to the azole group of antifungals. The variations are caused by different subgroups (ie, fluconazole and itraconazole are triazoles, with 3 nitrogen atoms, whereas ketoconazole is an imidazole containing 2 nitrogen atoms in a 5-membered azole ring [18].
Another unique case of cross-sensivity was observed in a 42-year old woman, who experienced FDE on fluconazole, a triazole, as well as on ornidazole, a new nitro imidazol antiprotozoal/antibacterial drug. She had not reacted to other nitro imidazole antiprotozoal/antibacterial drugs, such as metronidazole, or other antifungals, such as, itraconazole, ketoconazole or isoconazole [19].

Databases

Table 2. Reports of fixed (drug) eruption with fluconazole in the databases of the Netherlands Pharmacovigilance Centre Lareb, the WHO- and Eudravigilance (EMA) database [20] [21] [22]

Database	Term	Number of reports	ROR (95% CI)
Lareb	Fixed Drug eruption*	13	319.5 (166.7- 612.4)
WHO	Fixed eruption**	63	5.5 (4.3-7.1)
Eudravigilance***	-	-	-

* The lower level term *Fixed(Drug) Eruption* is used instead of the general preferred term *Drug Eruption* in the MEdDRA set
** The WHO-art *Fixed Eruption* is used instead of the general preferred term *Drug Eruption* in the MEdDRA set
*** No data from the Eudravigilance database are retrieved, because there is no possibility to search on the MEdDRA lower level term *Fixed (Drug) Eruption*. It is not useful to search on the preferred term *Drug Eruption.*

Prescription data

Table 3. Number of patients using fluconazole in the Netherlands between 2009 and 2013 [23]

Drug	2009	2010	2011	2012	2013
fluconazole	143,260	142,370	142,300	139,870	128,420

Mechanism

The pathogenic mechanism of FDE is not completely elucidated, but the condition is assumed to be caused by a delayed (type IV) allergy. Sensitisation may occur a few weeks to several years after starting the medication. Histologically, lesions show mononuclear infiltrate along the dermo-epidermal junction. Effector memory CD8+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 [2,5,8]
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 [24] [15].

Discussion and conclusion

Lareb has received 13 reports of fixed drug eruption with various expressions on different body parts 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, with a range between two and eight recurrences. In two patients (B, D) biopsy results confirmed the diagnosis. In four other cases (B,E,G, I) reporting was done by a dermatologist, therefore a reliable diagnosis was assumed. In most cases symptoms started within hours to days after administration of fluconazole. There were no other known confounding factors present in all cases, except possibly in one case (M), in which also amoxicillin was used.
There were no reports in the Lareb database of fixed drug eruption for the other triazole derivates.
The association is supported by a disproportionally number of reports of fixed eruptions on fluconazole in the WHO database and a substantial amount of publications upon this association in the literature.
It is of importance to acknowledge the possible role of fluconazole in a patient with fixed drug eruption, especially when it is located on the lip, where it mimics a herpes lesion. In

this situation antiviral treatment should not be initiated, but discontinuation of fluconazole results in a substantial improvement in symptoms.
Therefore, fixed drug eruption should be listed in the SmPC of fluconazole. Fixed drug eruption is a specific diagnosis, which is different from the already included adverse reaction drug eruption.

- Fixed drug eruption should be mentioned in the SmPC of fluconazole

References

1. Dutch SmPC Diflucan®. (version date: 29-12-2011, access date: 20-10-2014) http://db.cbg-meb.nl/IB-teksten/h13038.pdf.
2. Mulder WMC, editor. Side effects in dermatology. Naarden: IMP; 2009.
3. Netherlands Pharmacovigilance Centre Lareb. Fluconazole and Fixed Drug Eruption. (version date: 20-10-2014, access date: 20-10-2014) http://www.lareb.nl/Signalen/kwb_2007_3_fluc.
4. Morgan JM, Carmichael AJ. Fixed drug eruption with fluconazole. BMJ 1994;308(6926):454
5. Ghislain PD, Ghislain E. Fixed drug eruption due to fluconazole: a third case. J Am.Acad.Dermatol. 2002;46(3):467
6. Lane JE, Buckthal J, Davis LS. Fixed drug eruption due to fluconazole. Oral Surg.Oral Med Oral Pathol.Oral Radiol.Endod. 2003;95(2):129-30.
7. Mahendra A, Gupta S, Gupta S, Sood S, Kumar P. Oral fixed drug eruption due to fluconazole. Indian J Dermatol.Venereol.Leprol. 2006;72(5):391
8. Benedix F, Schilling M, Schaller M, Rocken M, Biedermann T. A young woman with recurrent vesicles on the lower lip: fixed drug eruption mimicking herpes simplex. Acta Derm.Venereol. 2008;88(5):491-4.
9. Wain EM, Neill S. Fixed drug eruption of the vulva secondary to fluconazole. Clin Exp.Dermatol 2008;33(6):784-5.
10. Jensen ZN, Bygum A, Damkier P. Fluconazole-induced fixed drug eruption imitating herpes labialis with erythema multiforme. Eur J Dermatol 2012;22(5):693-4.
11. Pai VV, Bhandari P, Kikkeri NN, Athanikar SB, Sori T. Fixed drug eruption to fluconazole: a case report and review of literature. Indian J Pharmacol. 2012;44(5):643-5.
12. Beecker J, Colantonio S. Fixed drug eruption due to fluconazole. CMAJ. 2012;184(6):675
13. Nakai N, Katoh N. Fixed drug eruption caused by fluconazole: a case report and mini-review of the literature. Allergol.Int 2013;62(1):139-41.
14. Walling HW, Swick BL. Cutaneous fixed drug eruption to fluconazole. J Drugs Dermatol 2010;9(8):1025-8.
15. Lester LJ, Brantley JS, Kelso RL, Kelly BC, Petitt MS, Wilkerson MG. Severe cutaneous adverse drug reaction due to fluconazole. J Drugs Dermatol 2008;7(11):1084-7.
16. Heikkila H, Timonen K, Stubb S. Fixed drug eruption due to fluconazole. J Am Acad Dermatol 2000;42(5 Pt 2):883-4.
17. Lareb. Fluconazol en fixed drug eruption. Geneesmiddelenbulletin 2009;43(5)
18. Gupta R, Thami GP. Fixed drug eruption caused by itraconazole: Reactivity and cross reactivity. J Am Acad Dermatol 2008;58(3):521-2.
19. Bavbek S, Yilmaz I, Sozener ZC. Fixed drug eruption caused by ornidazole and fluconazole but not isoconazole, itraconazole, ketoconazole and metronidazole. J Dermatol 2013;40(2):134-5.
20. Lareb database. (version date: 20-10-2014, access date: 20-10-2014) http://www.lareb.nl/.
21. WHO database Vigimine. (version date: 20-10-2014, access date: 20-10-2014) https://tools.who-umc.org/webroot/ (access restricted).
22. Eudravigilance database. (version date: 7-11-2014, access date: 7-11-2014) http://bi.eudra.org (access restricted).
23. GIP database - Drug Information System of the Dutch Health Care Insurance Board. (version date: 7-3-2014, access date: 12-10-2014) http://www.gipdatabank.nl/.
24. Mulder WMC, Meinardi MMHM. Als ons immuunsysteem ons parten speelt. Pharm Weekbl 2002;137(49):1752-7.

This signal has been raised on March 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl