1.1. Doxycycline and fixed drug eruption

Introduction

Doxycycline is an antibiotic belonging to the group of tetracyclines. It has a bacteriostatic effect against a broad spectrum of gram positive and gram negative bacteria. The indications of the oral preparation include *infections of the respiratory tract including infections with atypical pathogens and exacerbations of chronic bronchitis, the veneral diseases Chlamydia trachomatis urethritis and Treponema pallidum infections, the skin disorder acne vulgaris, Borrelia burgdorfori infections, and gastrointestinal cholera infections.*
The mechanism of action is inhibition of the bacterial protein synthesis by attachment to the 308 ribosomal subunit.
Doxycycline was granted marketing authorization in the Netherlands in 1982 [1].

Fixed drug eruption (FDE) is a mucocutaneous drug reaction located most often on the lips, genitalia or extremities. FDE characteristically reoccurs in the same locations upon re-exposure to the causing drug. In most cases the FDE leaves a post inflammatory hyperpigmentation after resolving. FDEs are immune-mediated. They appear as annular, oedematous, sometimes blistering, reddish-brown to violaceous macules or plaques, with an acute onset. FDE is usually mild and localized. There are rare severe atypical variants of FDE though, including multiple, non-pigmenting, and generalized bullous variants, which share clinical features with Stevens-Johnson syndrome/toxic epidermal necrolysis. The lesions generally appear 30 minutes to 8 hours after drug administration, but it can occur up to two weeks after drug exposure. When the culprit drug is discontinued, lesions resolve spontaneously in 7 to 10 days. There are many drugs that may induce FDE. Drug groups most frequently implicated are antibiotics, NSAIDS, paracetamol, barbiturates and antimalarials [2-4].

Reports

From 9 Augustus 1994 until 27 January 2016 the Netherlands Pharmacovigilance Centre Lareb received 27 reports suspect for FDE. In 2 of these reports (reports A and G) the reporter specifically reported FDE. In 8 reports the patient had experienced the same reaction in the past, being highly indicative for FDE (reports B, C, D, E, F, H, I and J). In all the 27 reports doxycycline was the only suspect drug. 12 reports concerned males, 14 females, and in one report unknown. The ages were between 19 and 75 years, mean 50 years, median 49 years. Latencies varied between 2 hours to 10 days, and in one report the latency was unknown. The most frequent locations were hands/wrists (13 reports), feet (4 reports), genitals (4 reports). There were 8 positive dechallenges (reports B, G, J, P, U, Y, Z, and AA that was treated with indifferent cream).

The 10 reports where the reaction FDE was reported, or where the patient had experienced the same reaction in the past are summarized in table 1.
In the other 17 reports, coded as bullous dermatitis (11 reports) or blisters (6 reports), it was not reported whether a similar reaction had occurred before, but the reaction FDE was very likely considering the described symptoms. These reports are summarized in table 2.

Table 1 Reports of fixed drug eruption and reoccurring blistering in the Lareb database

ID ,sex, age, source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reactions	Time to onset, action with drug, outcome
A 9551 F, 11-20 years, General Practitioner, through MAH	doxycycline tablet 100mg, 1 dd1, ?		Fixed eruption	2 Days Drug withdrawn Unknown
B 20249 F, 31-40 years, General Practitioner, through MAH	doxycycline 100mg, 1 dd1, ?	ethinylestradiol/ levonorgestrel	Fixed eruption	< 1 Day Drug withdrawn, Recovered (weeks)
C 23741 M, 41-50 years, Social medicine,	doxycycline tablet 100mg, 1 dd1 Acute sinusitis, unspecified		Fixed eruption	3 Days Drug withdrawn Unknown

through MAH				
D 25118 M, 61-70 years, General Practitioner, through MAH	doxycycline 100mg, 1 dd1 Upper respiratory infection	salbutamol budesonide	Fixed eruption	3.1 Hours Drug withdrawn Unknown
E 47507 F, 41-50 years, General Practitioner	doxycycline tablet 100mg, 1 dd 1 Acute sinusitis		Fixed eruption	1 Day Drug withdrawn Unknown
F 143748M, 51-60 years, Specialist doctor	doxycycline 100mg, 100 1 dd1 Lyme disease	omeprazol	Drug eruption	3 Hours Drug withdrawn Recovered/resolved
G 166665 F, 31-40, year, Specialist doctor	doxycycline 100mg, 1 dd1 Lyme disease		Drug eruption	10 Days Drug withdrawn Recovered/resolved
H 150230 M, 41-50, year, General Practitioner	doxycycline 100 mg,1dd1	fluticasone salbutamol	Blister	1 Day Drug withdrawn Recovering/resolving
I 151891 M, 41-50 years, General Practitioner	doxycycline tablet 100mg, 1dd1 Respiratory infection		Blister Skin reaction Swelling of the feet	5 Hours Drug withdrawn Not recovered
J 101298 M, 61-70 years, General Practitioner	doxycycline 100 mg, sinusitis, bronchitis	triamcinolon formoterol/ budesonide	Haematoma Allergic vasculitis? Purpura	1 Day Drug withdrawn Recovered

A: No further description.
B: Red spot on the palms of the hand, itching, with dark bruise in the middle. The complaints lasted for a week and then disappeared.
During a previous course in the past, the patient experienced exactly the same symptoms.
C: Red spots with blood blisters on the glans penis (status after circumcision) and also two red spots in the neck. The same reaction had occurred 3 to 4 years before when using doxycycline for a week because of sinusitis.
D: Pruritus of the penis, nowhere else on the body. About one and a half year before, the patient experienced the same reaction to the same medication, then treated with miconazole cream.
E: Burn-like lesion on the feet. Four years before current reaction, the patient experienced the same reaction but only very locally (about 5x4 cm) after using doxycycline for a short period. The reporter mentioned that the reaction appeared like very localized Stevens Johnson's syndrome.
F: Allergic reaction of the foreskin of the penis. Four years ago, the patient experienced the same reaction during a course of doxycycline. The reaction was treated with clobetasol.
G: No further description. The patient used the drug in the past without a similar reaction. The reporter mentioned that the fixed drug eruption was confirmed by allergological investigation.
H: Genital blisters. The patient used doxycycline in the past and also experienced genital blisters. The reaction was treated with miconazole.
I: Oedema and blisters under both feet (3 cm diameter) without systemic effects. The patient used doxycycline in the past and also experienced blisters only on the feet. Current reaction occurred quicker than the previous time.
J: Subcutaneous small bleedings / blood blisters on the fingers. About one year and 4 months before current reaction the patient experienced the same symptoms, one day after intake of doxycycline.

Table 2. Reports of dermatitis bullous and blisters where reoccurrence was not reported, but symptoms being indicative for FDE, in the Lareb database

ID, Sex, age, source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reactions	Time to onset, action with drug, outcome
K 5451 M, 41-50 year, General Practitioner, through MAH	doxycycline 100mg, 1 dd1, unknown		Dermatitis bullous	6 Hours Drug withdrawn Unknown
L 10823 M, 51-60 years, Pharmacist, through MAH	doxycycline 100mg1 dd 1 Acute sinusitis, unspecified		Dermatitis bullous	2 Hours Drug withdrawn Unknown
M 14967 M, 41-50 years, General Practitioner, through MAH	doxycycline 100mg, 1 dd 1, Bronchitis acute NOS	diclofenac cimetidine zolpidem	Dermatitis bullous	1 Day Drug withdrawn Unknown
N 15699 F, 61-70 years, Pharmacist, through MAH	doxycycline 100mg, 1 dd 1, Upper respiratory infection		Dermatitis bullous	5 Days Drug withdrawn Unknown
O 23643 F, 51-60, year, General Practitioner, through MAH	doxycycline 100mg, 1 dd 1, Bronchitis acute NOS		Dermatitis bullous	Less than a day Drug withdrawn Unknown
P 31713 M, 41-50, year, General Practitioner, through MAH	doxycycline 100mg, 1 dd 1, unknown		Dermatitis bullous	4 Days Drug withdrawn Recovering
Q 37061 F, 31-40 year, General Practitioner, through MAH	doxycycline 100mg, 1 dd1 Bacterial infection NOS		Dermatitis bullous	1 Day Drug withdrawn Not recovered
R 47803 Unknown, 71 years and older, General Practitioner	doxycycline 100mg, 1 dd2 Bacterial infection NOS eye	acenocoumarole bisoprolol bumetanide perindopril digoxine	Dermatitis bullous Dermatitis	Hours Drug withdrawn Unknown
S 75017 M, 41-50, year, Consumer	doxycycline 100 mg 1dd1 Chronic bronchitis		Dermatitis bullous	2 Hours Drug withdrawn Recovering
T 78224	doxycycline		Dermatitis bullous	10 Days

F, 51-60 years, General Practitioner	100mg, 100 mg, 2dd1 Lyme disease		Neuralgia (neuropathy of the shine and elbow)	Drug withdrawn Recovering
U 169484 M, 71 years and older, General Practitioner	doxycycline 100mg, 1 dd1 Upper respiratory tract infection		Dermatitis bullous	4 Days Drug withdrawn Recovering
V 110331 F, 41-50 years, General Practitioner	doxycycline 100mg, 1dd1	budesonide/formoterol ethinylestradiol / desogestrel	Blister	Days Drug withdrawn Unknown
W 120784 F, 51-60 years, Pharmacist	doxycycline 100mg, 1 dd1 Respiratory infection	irbesartan/hydrochlorothiazide metoprolol nifedipine	Blister	6 Hours Drug withdrawn Recovering
X 126447 F, 51-60 years, General Practitioner	doxycycline, 100 mg, 1dd1 Lyme disease		Blister	3 Days Drug withdrawn Not recovered
Y 163157 F, 31-40 years, General Practitioner	doxycycline 100 mg 1dd1 Bronchitis	ethinylestradiol/desogestrel, ipratropium	Blister	1 Day, Drug withdrawn Recovered
Z 173723 F, 41-50 years, Pharmacist	doxycycline, 200 mg, 1dd1		Erythema Blister Pyrexia	Unknown Unknown Recovering
AA 207524 F, 61-70 years, General Practitioner	doxycycline 100 mg 2 dd1, Respiratory infection	hydrochlorothiazide, tiotropium	Blister	Less than 1 day Drug withdrawn Recovering

K: Redness with blistering of the right hand palm.
L: Purple blisters filled with fluid on the hands, hip and foot.
M: Bullae with peripheral erythema on both hands.
N: Blistering and itching, on the wrists and on the tongue.
O: Two blisters on the natal cleft.
P: Bullae on the hand.
Q: Blister on the left wrist.
R: Bulla on the abdominal skin and local dermatitis.
S: Red hands with blisters and severe itching. The reaction was treated with 2 drugs.
T: Erythema and blisters on the nose, tongue, lips, index fingers on both sides and big toe. The reaction was treated with antihistaminic and betamethasone cream on the hands.
U: Bullous abnormalities in the mouth, sort of inflammations, no pus, it concerned raised patches, no sores.
V: Blisters on the hands.
W: Blisters (3-4 cm) and severe itching on one hand. The reaction was treated with levocetirizine and binding.
X: Blisters.
Y: Blisters on the face and legs.
Z: Red spots with blisters, fever. The reporter mentioned the patient had not been sitting in the sun, and the symptoms were mainly located on the parts of the body that are covered by clothes.
AA: Blistering. On a photo that was added to the report red / purple spots / blisters were visible on the index finger and thumb. The reaction was treated with vaseline.

Other sources of information

SmPC

The Dutch SmPC of doxycycline does not mention FDE or blisters as an adverse reaction. The SmPC does describe maculo-papular and erythematous rash, photosensibility, erythema multiforme, Stevens-Johnson's syndrome, toxic epidermal necrolysis, and exfoliative dermatitis as adverse drug reactions [1].

Literature

Tetracyclines are described in the literature to cause FDE [3,5-7].
A recent study in Singapore in 62 definite or probable FDE cases, doxycycline was the culprit drug in 3 patients (4.8%) [8].
Furthermore a case report was described of a 37-year old female with blisters on the face, chest, abdomen, both arms, forearms, back, thighs and around eyelids, one day after administration of doxycycline. Her medical history indicated doxycycline with rashes over the trunk as a reaction in the past. She was treated with several drugs and recovered [9].
Another case-report concerned a 49 year old male with recurrent, hyperpigmented patches of the hands and the penis, with irregular use of doxycycline because of brucellosis. The diagnosis FDE was confirmed by biopsy [10].
Furthermore the association is described on the website "Huidziekten" [Skin diseases], a leading website for dermatologists in the Netherlands [11].

Databases

Table 3. Reports of the coded PT "Drug eruption" associated with doxycycline, in the Lareb [12], WHO [13] and Eudravigilance database [14].

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Drug eruption	7	15.0 (6.9-32.7)
WHO	Drug eruption	398	11.8 (10.6-13.0)
Eudravigilance	Drug eruption	48	4.7 (3.5-6.2)

Prescription data

Table 4. Number of patients using doxycycline in the Netherlands between 2010 and 2014 [15].

Drug	2010	2011	2012	2013	2014
Doxycycline	933,230	878,230	818,990	735,110	663,320

Mechanism

The exact pathogenic mechanism of FDE is not completely elucidated, but it is assumed that FDE is caused by a delayed (type IV) allergy. Intra-epidermal $CD8^+$ T cells are assumed to have a key role in mediating the localized epidermal lesion
The recurrence on the same location may be explained by prolonged ICAM-1 expression in the lesional keratinocytes, which were found to correlated with the degree of residing epidermal T suppressor/cytotoxic cells [16].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 27 cases that were suspect for fixed drug eruption. In 2 cases FDE was reported, and in 8 cases the patient had experienced the same reaction in the past, being highly indicative for FDE. In the other 17 cases it was not reported whether a similar reaction had appeared in the past, but this might very well have been the first manifestation of FDE. In these cases the symptoms were highly compatible with FDE, and this together with the positive

dechallenges, make other possible diagnoses like bullous pemphigoid or erythema multiforme less likely. In all the cases doxycycline was the only suspect drug. Another strong aspect were the short latencies after exposure, varying from 2 hours to 10 days, compatible of what is known of FDE, and the great number of 8 positive dechallenges that were reported.
Weak aspects that in one case confirmation by allergological investigation was described, but in none of the reports histology was described. Another weak aspect was that none of the cases described post inflammatory hyperpigmentation after recovery. Post inflammatory hyperpigmentation does not occur in all FDE cases though, and maybe people might have interpreted this as a part of a normal healing reaction.
Based on the strong reports received by Lareb, it is suggested that doxycycline may have a causative role in the occurrence FDE. Therefore FDE should be mentioned in the SmPC of doxycycline.

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

References

1. Dutch SmPC Doxycycline 100 mg PCH, omhulde tabletten 100 mg. (version date: 9-2-2015, access date: 27-1-2016) http://db.cbg-meb.nl/IB-teksten/h09519.pdf.
2. Mulder W. Side effects in dermatology. Naarden IMP, 2009.
3. UpToDate. Fixed drug eruption. (version date: 2016, access date: 27-1-2016) http://www.uptodate.com/contents/fixed-drug-eruption?source=machineLearning&search=fixed+drug+eruption&selectedTitle=1%7E48&sectionRank=1&anchor=H1633162#H1633162.
4. Duarte de Sousa IC. Images in clinical medicine. Fixed drug eruption. N Engl J Med 2016;2011(Aug 11):365(6):e12
5. Walfish AE, Sapadin AN. Fixed drug eruption due to doxycycline and metronidazole. Cutis 2002;(69):207-8.
6. Tham SN, Kwork YK. Cross-reactivity in fixed drug eruptions to tetracyclines. Arch Dermatol. 1996;(132):1134-5.
7. Correia O, Delgado L, Polonia J. Genital fixed drug eruption: Cross-reactivity between doxycycline and minocycline. Clin Exp Dermatol. 1999;(24):137.
8. Heng YK, Yew YW, Lim DS, Lim YL. An update of fixed drug eruptions in Singapore. J Eur Acad Dermatol Venereol. 2015;29(8):1539-44.
9. Nitya S, Deepa K, Mangaiarkkarasi A, Karthikeyan K. Doxycycline induced generalized bullous fixed drug eruption - A case report. J Young Pharm. 2013;5(4):195-6.
10. Gul U, Gonul M, Soylu S, Kaya I. Doxycycline-induced fixed drug eruption. J Dermatol Treat 2008;19(2):126-7.
11. Dutch Website "Huidziekten" [Skin diseases]. (version date: 2016, access date: 15-2-2016) http://www.huidziekten.nl/zakboek/alfabet/alfabetframef.htm.
12. Lareb database. (version date: 2014, access date: 27-1-2016) http://www.lareb.nl/Bijwerkingen/Zoek-op-geneesmiddel.
13. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2014, access date: 27-1-2016) https://tools.who-umc.org/webroot/ (access restricted).
14. Eudravigilance database. (version date: 2014, access date: 27-1-2016) http://bi.eudra.org (access restricted).
15. College for Health Insurances. GIP database. (version date: 7-3-2014, access date: 27-1-2016) http://www.gipdatabank.nl/.
16. Lee AY. Fixed drug eruptions. Incidence, recognition, and avoidance. Am J Clin Dermatol. 2000;1(5):277-85.

This signal has been raised on April 2016. 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