

## Doxycycline and photo-onycholysis – an update

### Introduction

Doxycycline is an antibiotic belonging to the group of tetracyclines. It is active against gram positive and gram negative bacteria. It has been on the Dutch market at least since 1973 and the oral preparation is indicated for *infections of the respiratory tract, infections of the urogenital tract, infections of the skin and soft tissues, Borrelia burgdorferi infections, infections of the gastrointestinal tract and eye infection in particular trachoma* [1-4].

Photodermatitis or photosensitivity is mentioned as an adverse drug reaction in the SmPC of doxycycline. The SmPC does not mention (photo-)onycholysis [1-4].

Photo-onycholysis refers to separation of the nail plate from the nail bed after exposure to ultraviolet light. Pain in the nail bed or tips of the fingers and toes is often the first symptom with subsequent progression to subungual erythema, subungual hemorrhage, and onycholysis. Pain and subungual erythema are infrequently the only manifestations at the time of presentation. Onycholysis develops after a variable period. Pain and tenderness seem to decrease as the nail changes become clinically evident [5].

In the Quarterly Report 2003-1 Lareb asked attention for the association between doxycycline and photo-onycholysis [6]. At the moment this Quarterly Report was written, the Lareb database contained three cases of photo-onycholysis in association with the use of doxycycline. Since 2003, Lareb has received nine more reports about this association and although photosensitivity is described in the SmPC, it is not clear to all reporters that this reaction can also include the nails. The current observation is an update of the signal sent to the MEB in the first quarter of 2003.

### Reports

On the 11<sup>th</sup> of January 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained 12 reports of photo-onycholysis associated with the use of doxycycline. The reports are listed in table 1.

Table 1. Reports of photo-onycholysis associated with the use of doxycycline

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 25961 M, 11-20 pharmacist	doxycycline 100mg 2dd	phenethicillin, thromethamine eardrops, triamcinolone cream	onycholysis, skin discolouration, photosensitivity reaction	5 weeks discontinued not reported
B 36931 F, 31-40 pharmacist	doxycycline 100mg 2dd	citalopram	onycholysis	3 days discontinued not recovered
C 37970 F, 31-40 general practitioner	doxycycline 100mg 2dd Lyme disease		onycholysis	week unknown recovered
D 41518 F, 8-10 general practitioner	doxycycline 100mg Lyme disease		onycholysis	3.5 weeks after start, 2.5 weeks after discontinuation not recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E 42017 F, 51-60 general practitioner	doxycycline 100mg Lyme disease		onycholysis, photosensitivity reaction, abdominal discomfort	2 weeks discontinued unknown
F 59708 F, 11-20 general practitioner	doxycycline 100mg 2 dd Lyme disease	levocetirizine, ethinylestradiole/levonorgestrel	onycholysis	10 days discontinued after 14 days unknown
G 83321 F, 51-60 specialist doctor	doxycycline 200mg 1 dd Tick bite		onycholysis	14 days discontinued before reaction occurred recovered
H 110387 F, 31-40 consumer	doxycycline 100mg 2dd Tick bite		onycholysis, pain localised	2 months no change recovered
I 126042 M, 8-10 general practitioner	doxycycline 100 mg 2dd Lyme disease		onycholysis, photosensitivity reaction	3 weeks discontinued unknown
J 139748 F, >71 pharmacist	doxycycline 100mg 1 dd Pneumonia	fluorouracil cream	onycholysis, nail discolouration	7 days not applicable not recovered
K 141868 F, 31-40 consumer	doxycycline 250 mg 2dd Lyme disease		onycholysis, abdominal discomfort	3 days no change not yet recovered
L 142155 M, 8-10 general practitioner	Doxycycline 100 mg 2dd Lyme disease		onycholysis	12 days no change unknown

Additional information about the cases is described below:

Patient A, a boy aged 11 – 20 years, developed a photosensitivity reaction in his face upon sunbathing with swelling and redness of his face, ears, lips and nose with a latency of twelve days after starting doxycycline. Also white spots arose on his cheeks, ears, nose and upper lip occurred. The doxycycline course was finished 2 days later. The patient developed onycholysis 3 weeks afterwards (5 weeks after starting doxycycline).

Patient B developed onycholysis 3 days after starting a doxycycline course. At first, one nail came off; 2 weeks later two other nails followed. The patient was on holidays and had been sunbathing. She did not develop any other adverse skin reactions. One month after finishing the doxycycline course, she was recovering.

Patient C developed severe pain in the nails several hours after starting doxycycline for Lyme disease. She was on holidays and was exposed to sunlight. During the continued doxycycline course (14 days) her nails became less painful, but the middle parts of the nails became disconnected from the skin. All finger nails were involved, plus 4 of the toenails. Onycholysis occurred in this patient as single adverse skin reaction. It took 5 months for her nails to recover.

Patient E experienced haematoma's under her nails. Her fingertips were very painful. Later a partial onycholysis occurred with discoloration of the nails. The patient knew that doxycycline could cause photosensitivity and had stayed in the shade and covered herself with clothing and a hat. For case E a picture is available of the what the patient's nails looked like, three months after doxycycline had been discontinued.

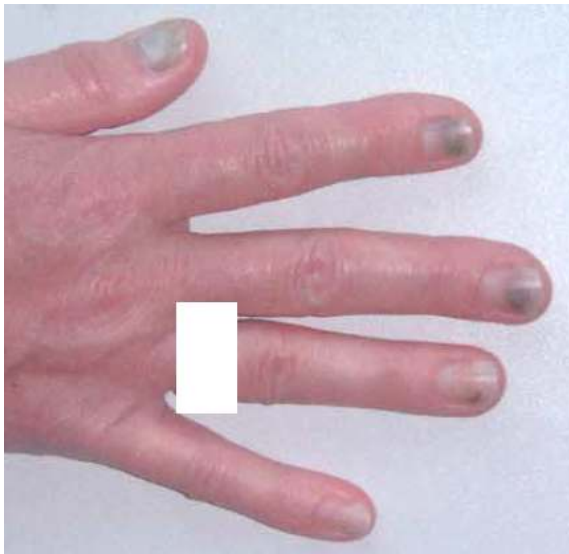


Figure 1: nails of patient E, 3 months after discontinuation of doxycycline

Patient G had been using a factor 50 sunblock. The reaction was treated with systemic betamethasone.

Patient H is a general practitioner who reported as a consumer. She used a sunblock with a high UV factor. During sun exposure she experienced pain of the nail beds of her thumbs, later onycholysis of her thumbnails occurred.

Patient I first experienced photosensitivity of the skin after sun exposure with a latency of two days after doxycycline was started. Doxycycline was then withdrawn and the patient was treated with an antihistaminic drug. After two weeks discoloration of the nails occurred, followed by onycholysis of all the fingernails and some of the toenails.

Patient J also used fluorouracil cream on the cuticle for the treatment of verruca vulgaris.

Patient K reported the following: "*Excruciating pain in the nails after using doxycycline and exposure to sunlight. The package leaflet only makes mention of possible problems of the skin after exposure to sunlight when using Doxy.*"

"...I'm very surprised that in all of this leaflet the patient isn't warned one time to use extra protection for the nails, for example gloves or something. My toenails are spared because I had painted them."

### Other sources of information

#### SmPC

Photodermatitis or photosensitivity is mentioned as an adverse drug reaction in the SmPC of doxycycline. The SmPC does not mention (photo-)onycholysis [1-4].

#### Literature

In 2004, The Netherlands Pharmacovigilance Centre Lareb described the first five reports concerning photo-onycholysis associated with the use of doxycycline in the BMJ [7]. In the literature several other cases of photo-onycholysis associated with doxycycline are described [5,8,9].

#### Databases

On January 11<sup>th</sup> 2013 the database of the Netherlands Pharmacovigilance Centre Lareb contained 12 reports of Preferred Term (PT) Onycholysis associated with the use of doxycycline, which was reported disproportionally (ROR = 11.4, 95% CI 3.6 – 36.3). The number of reports and disproportionality for the WHO database of the Uppsala Monitoring Centre and the Eudravigilance database are given in table 2.

Table 2. Reports of onycholysis with doxycycline in the databases of the Netherlands Pharmacovigilance Centre Lareb and the WHO- and Eudravigilance (EMA) database.

Drug	Number of reports	ROR (95% CI)
Doxycycline	Lareb: 12	70.7 (35.1 – 142.5)
	WHO: 43	51.4 (37.6 – 70.2)
	EMA: 10	21.4 (22.0 – 78.0)

### Prescription data

The number of patients using doxycycline in the Netherlands is shown in table 3.

Table 3. Number of patients using doxycycline in the Netherlands between 2007 and 2011 [10].

Drug	2007	2008	2009	2010	2011
Doxycycline	961,250	982,260	965,820	933,230	880,750

### Mechanism

The mechanism of the phototoxic (nail) reaction caused by doxycycline has not been fully elucidated. It is believed to be mediated by excited-state singlet oxygen and free radicals after irradiation with ultraviolet A radiation, thereby causing selective injury to mitochondria, within which doxycycline and other tetracyclines are localized [11].

A number of possible explanations for why the nails should be a site of predilection for phototoxic damage in some patients have been proposed. Irradiation with 313- to 500-nm wavelengths (3%–20%) can penetrate a 0.7-mm fingernail plate. There is less melanin and, therefore, less ultraviolet protection in the nail beds than in other sites. It is also possible that application of chemical sunscreen may afford sufficient photo-protection for exposed areas of skin while leaving the nail bed unprotected [5].

The cause of the intense pain during the early stages of the process is unclear but may be related to vasodilation of the nail bed capillaries [5].

### Discussion and conclusion

The association between doxycycline and photo-onycholysis has been reported to Lareb 12 times and is supported by a statistically significant disproportionality in the Lareb-, WHO- and Eudravigilance database, as well as cases in the literature [5,7-9] and a possible pharmacological mechanism.

It is suggested that patients with skin types 1 and 2 (light and fair skin) may be more susceptible to doxycycline photosensitivity than patients with darker skin pigmentation [5]. However, Lareb has no information about the patient's skin type, except for patient E for which a picture is available.

The adult dosage of doxycycline is 200 mg the first day of treatment, followed by 100 mg (1 tablet) daily. In the treatment of severe infections (for instance chronic infections of the urinary tract), the dose should be increased to 200 mg per day. *Borrelia burgdorferi* infections can be treated with 200 mg per day for 10-21 days (early phase of the disease) up to 1 month in more severe cases [1]. Almost all patients who experienced photo-onycholysis used doxycycline for (prevention of) Lyme disease's, where a higher dosage per day is indicated than for other infections. The fact that most patients used this higher dosage possibly indicates that the photo-onycholysis is a dosage dependent effect.

No studies were found that suggested a possible connection between Lyme disease and onycholysis.

Based on the available information for this association, photo-onycholysis should be explicitly mentioned in the SmPC of doxycycline in addition to the photodermatitis/photosensitivity reactions.

- Photo-onycholysis should be mentioned in the SmPC of doxycycline

## References

1. Dutch SmPC Doxycycline 100 mg PCH, omhulde tabletten 100 mg. (version date: 12-4-2012, access date: 16-1-2013) <http://db.cbg-meb.nl/IB-teksten/h09519.pdf>.
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3. Dutch SmPC Doxycycline dispergeerbaar ratiopharm 100 mg, tabletten. (version date: 21-5-2012, access date: 16-1-2013) <http://db.cbg-meb.nl/IB-teksten/h16491.pdf>.
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*This signal has been raised on May 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB [www.cbgmeb.nl/cbg/en/default.htm](http://www.cbgmeb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).*