

## **Doxycycline and skin discoloration**

### **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 skin discoloration or skin hyperpigmentation [1-4].

Melanocytes are derived embryonically from neural crest cells that migrate into the basal layer of the epidermis. In the skin, melanocytes continuously produce melanosomes, organelles that are transferred to keratinocytes. The melanosomes convert tyrosine to melanin, giving skin its color. Under the stimulus of hormones or irritation, the production of melanosomes increases, leading to hyperpigmentation. In response to sun exposure or idiopathically in some disorders, activation of melanocytes occurs and causes hyperpigmentation. The same melanocyte concentration is present in persons of all races who have normal skin. However, some races have larger melanosomes, giving their skin a darker colour [5]. Drug-induced pigmentation represents 10 to 20% of all cases of acquired hyperpigmentation [6]. Overall, several mechanisms for drug-induced pigmentation have so far been described [6,7] and these mechanisms are not mutually exclusive.

Firstly, the accumulation of melanin, either free in the dermis or contained mainly within cutaneous cells particularly the dermal macrophages rather than in the basal layer of the epidermis. This melanin accumulation usually results from either hyperproduction by epidermal melanocytes specifically stimulated by the medication or in response to a nonspecific cutaneous inflammation linked to the drug itself. This mechanism is very often worsened by sun exposure.

Secondly, the accumulation of the triggering medication itself, without any association to melanin, usually appearing as granules freely scattered among extracellular matrix elements or included within dermal macrophages that are unable to eliminate these foreign bodies.

Thirdly, the synthesis of special pigments, such as lipofuscin, probably under the direct influence of the drug.

Lastly, the deposition of iron, usually resulting from drug-induced damage to dermal vessels with leakage of red blood cells and subsequent lysis throughout the dermis [6].

### **Reports**

The Netherlands Pharmacovigilance Centre Lareb received 5 reports of skin discoloration/hyperpigmentation associated with the use of doxycycline in a period from 01-10-1999 until 21-06-2013. The reports are listed in table 1.

Table 1. Reports of skin and nail discoloration 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 156211 M, 71 years and older Specialist doctor	doxycycline 3 dd 100 mg Chronic Q-fever and infected vessel prosthesis	acetylsalicylic acid, esomeprazole, levothyroxine sodium, nebivolol, atorvastatin	skin hyperpigmentation	9 months discontinued not recovered
B 156212 M, 71 years and older Specialist doctor	doxycycline, about 4 months 200 mg daily, the next 6 months 300 mg daily Chronic Q-fever	acetylsalicylic acid, omeprazole, ferrous fumarate, celecoxib, tamsulosine with dutasteride, prednisolone, azathioprine, hydroxy- chloroquine, simvastatin.	hyperpigmentation skin	10 months discontinued not recovered
C 102886 F, 61-70 years Pharmacist	doxycycline 100mg start 2dd, furthermore once daily 100 mg Respiratory infection		discoloration skin	2 days discontinued recovered
D 51212 F, 31-40 years General Practitioner	doxycycline 100mg 1dd Lower respiratory tract infection	perindopril	hyperpigmentation skin	2 weeks discontinued unknown
E 60201 M, 61-70 years Pharmacist	doxycycline 100mg 1dd Infection		photosensitivity reaction, pigmentation abnormal	9 days after start, 2 days after cessation discontinued not recovered

Additional information about the cases is described below:

Cases A and B were reported by the same Specialist doctor.

In case C it is described that the skin was black as coal and smooth, there was no itching or any other symptom. The patient has a light tinted skin color. The latency period described in this case is short, so possibly sun exposure is a causative factor.

In case D the hyperpigmentation of the skin was located in the face. There were brown, not sharply defined, maculae on the forehead. The patient does not have a history of skin disorders or naevi and she is not pregnant.

In case E the patient went on a holiday in the sun two days after doxycycline was withdrawn. During the course the patient stayed out of the sun but it was unknown to him that he should do so when the course had ended. He now has severe and lasting hyperpigmentation on his nose.

In addition, Lareb received three reports of nail discoloration associated with the use of doxycycline. In two cases the patient also suffered from onycholysis. These cases are described in Quarterly Report 2013-2 'Doxycycline and photo-onycholysis – an update' [8] as Case A (Reportnumber 25961) and case J (Reportnumber 139748). Additional report 71069 from a pharmacist concerns a female aged 51-60 years years, with nail discoloration following administration of doxycycline (dose twice daily 100 mg) for Lyme's disease with a latency of two months after start. Doxycycline was withdrawn. The patient outcome is unknown.

Because we could not be certain that the nail discoloration is not a result of the onycholysis in the first two cases, the focus of this signal was placed on discoloration of the skin and not the nails.

## 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 skin or nail hyperpigmentation [1-4].

## Literature

Hyperpigmentation of the oral cavity (teeth, mucosa, alveolar bone), skin, nails, eyes, thyroid and even bone has been reported due to minocycline intake [9-11]. Also for other tetracyclines hyperpigmentation of the skin has been described, albeit to a lesser extent than for minocycline [12-14]. Pichardo *et al.* [14] reported on a 44-year old man who had been treated with doxycycline for three years, 100 mg twice daily for chronic follicular conjunctivitis. For the last six months he suffered from progressive, symmetric blue-gray periocular discoloration. A biopsy from lesional skin showed granular deposits of a brown to black pigment in the superficial dermis. Eight months after cessation of doxycycline, the patient had almost completely recovered.

Nail discoloration induced by doxycycline has also been described. Akcam *et al.* [15] report on an 11-year-old-boy with nail discoloration caused by doxycycline intake who was referred to their hospital for evaluation. The history revealed that, in April 2004, the patient had brucellosis that was treated with doxycycline 200 mg on the first day and 100 mg daily thereafter, combined with gentamicin for 10 days. Doxycycline therapy was stopped because he developed photosensitivity. The symptoms of brucellosis resolved, but brown discoloration of the nails developed after 15 days of doxycycline intake. Physical examination revealed painless brown discoloration of the fingernails. The oral cavity and teeth had no changes in colour. The laboratory findings revealed normal hematologic and biochemical results. The nail discoloration disappeared in one month.

## Databases

Table 2. Reports of skin discolouration/hyperpigmentation with doxycycline in the databases of the Netherlands Pharmacovigilance Centre Lareb and the WHO- and Eudravigilance (EMA) database [16,17].

Database	Preferred Terms	Number of reports	ROR (95% CI)
Lareb	Skin hyperpigmentation	3	3.6 (1.1-11.4)
	Skin discolouration	1	-
	Pigmentation disorder	1	-
	Total	5	1.2 (0.5-3.0)
WHO	Skin hyperpigmentation	17	3.6 (2.2-5.7)
	Skin discolouration	45	1.3 (1.0-1.8)
	Pigmentation disorder	14	3.9 (2.3-6.7)
	Total	76	1.8 (1.5-2.3)
Eudravigilance	Skin hyperpigmentation	8	8.5 (4.2 – 17.1)
	Skin discolouration	19	3.6 (2.3 – 5.6)
	Pigmentation disorder	5	4.4 (1.8 – 10.6)
	Total	32	4.4 (3.1 – 6.2)

### Prescription data

Table 3. Number of patients using doxycycline in the Netherlands between 2009 and 2013 [18].

Drug	2009	2010	2011	2012	2013
Doxycycline	965,820	933,230	878,230	819,780	739,860

### Mechanism

Skin hyperpigmentation induced by minocycline is a well-recognized side effect but has rarely been reported for other tetracyclines. Several types of minocycline-induced hyperpigmentation of the skin have been distinguished based on distinct clinical features and their histopathologic correlates. The first type is characterized by blue-black pigmentation within areas of scars and previously inflamed skin; in the second type, blue-gray pigment spots develop in normal skin, especially on the shins and arms; and the third type is characterized by a muddy-brown generalized pigmentation, mostly accentuated in sun-exposed areas [6,19]. This third type is likely caused by increased melanin or melanin–minocycline complexes at the dermal–epidermal interface [9]. Patient E reported to Lareb the hyperpigmentation occurred after exposure to the sun, which is also described for the third type of minocycline induced skin discoloration. Based on a previously reported unusual case of chronic doxycycline abuse of twelve years in a psychotic patient [13], Böhm *et al.* [19] have investigated the nature of the observed pigment changes in the same patient. The histomorphologic and ultrastructural changes induced by doxycycline shared several features with cutaneous hyperpigmentation caused by minocycline. The biophysical findings further suggest a direct deposition of doxycycline, probably chelated with iron and/or calcium, within the lesional skin. The authors mention that in the present case a prolonged suprapharmacologic dosage of doxycycline was used, but that physicians should watch for pigment changes in patients receiving long-term therapy.

### Discussion and conclusion

The association between doxycycline and skin hyperpigmentation has been reported to Lareb 5 times and is supported by a statistically significant disproportionality in the WHO- and Eudravigilance database, as well as cases in the literature [13,14] and a possible pharmacological mechanism [19]. In addition, Lareb received three reports of nail discoloration associated with doxycycline use. However, two of these patients also suffered from onycholysis and it's unclear if this was also the cause of the discoloration. Nail discoloration induced by doxycycline has also been described [15].

Risk factors for tetracycline-induced pigmentary changes include the duration of treatment, the cumulative dose (risk high above 50g) the presence of previous skin alterations related to inflammation or excessive sun exposure or the concomitant intake of other pigmentation-inducing medications [6].

Böhm *et al.* [19] have speculated on the reason for the apparently much higher incidence of hyperpigmentation caused by minocycline compared with doxycycline. Minocycline is the classic antibiotic for patients with acne or rosacea and may be prescribed for several years. Doxycycline is more commonly used for acute bacterial infections is usually given for shorter periods. However, case A and B reported to Lareb used doxycycline chronically for months.

According to Böhm *et al.* [19] the apparently higher incidence of pigment changes in patients taking minocycline may also be the result of differences in the chemical structures of minocycline and doxycycline. Doxycycline has a hydroxyl group at position 5 and a methyl group at position 6, whereas minocycline carries a para-N, N-dimethylamino group at position 7 of the naphthacene carboxamide ring. These

structural differences create a number of changes in the physicochemical properties of both tetracyclines. For instance, minocycline is twice as lipophilic as doxycycline and penetrates more easily in tissues.

For minocycline it has been described that pigmentation of the skin and nails may require months to years to fade after discontinuation of the drug, and other sites may remain permanently discoloured [10]. For doxycycline Lareb has also received cases of patients who had not recovered from the hyperpigmentation at the moment of reporting.

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

- Skin discoloration should be mentioned in the SmPC of doxycycline

## References

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*This signal has been raised on October 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.cbqmeb.nl/cbq/en/default.htm](http://www.cbqmeb.nl/cbq/en/default.htm)*