

Doxycycline and paraesthesia

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].

Paraesthesia is defined as an abnormal sensation, such as burning, pricking, tickling, or tingling. Paraesthesias are one of the more general groupings of nerve disorders known as neuropathies [5]. Paraesthesia is not described in the SmPC of doxycycline [1-4].

This observation describes the association between doxycycline and paraesthesia.

Reports

On the 16th of January 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained 13 reports of paraesthesia associated with the use of doxycycline. The reports are listed in table 1.

Table 1. Reports of paraesthesia associated with the use of doxycycline

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 5749 M, general practitioner	doxycycline 100mg 1dd	prednisolone	paraesthesia	1 hour no change not reported
B 18359 F, 21-30 specialist doctor	doxycycline 100mg 2dd	ethinylestradiole/ levonorgestrel	paraesthesia	2 days discontinued not reported
C 18878 F, 11-20 pharmacist	doxycycline 100mg 1dd	cromoglicic acid nasal spray, loratadine, budesonide, ibuprofen	paraesthesia distal	3 days discontinued not reported
D 41317 F, pharmacist	doxycycline 100mg 2dd Lyme disease	anastrozole	paraesthesia	7 days discontinued recovered
E 47751 F, 41-50 specialist doctor	doxycycline 100mg 2dd Lyme prophylaxis		paraesthesia	8 days discontinued unknown
F 52140 F, 21-30 hospital pharmacist	doxycycline 100mg 2dd Lyme disease		paraesthesia, anxiety, nightmares	1 week discontinued recovered
G 66621 M, 61-70 general practitioner	doxycycline 100mg Rosacea	atorvastatin, omeprazole, metronidazole cream	electric shock sensation, arthralgia	5 days discontinued recovered

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
H 90448 M, 61-70 physician	doxycycline 100mg Lyme disease		paraesthesia, photosensitivity reaction, photophobia	2 days discontinued recovered
I 105057 M, 41-50 consumer	doxycycline 100mg od Acute bronchitis		paresthesia, diarrhoea, pruritus	6 days unknown recovering
J 145022 F, 51-60 specialist doctor	doxycycline 100mg Lyme disease		hypersensation skin, paraesthesia hand	4 days discontinued recovered
K 109954 F, 61-70 consumer	doxycycline 100mg od Sinusitis	verapamil, desloratadine	paresthesia hand, oedema hands	1 hour discontinued not recovered
L 55689 M, 51-60 general practitioner	doxycycline 100mg od Sinusitis		paraesthesia, oedema, rash, skin ulceration	1 week discontinued recovered
M 74538 F, 21-30 specialist doctor	doxycycline 100mg od Allergy test		paraesthesia distal, edema hands, dizziness, macular rash, pruritus, hyperhidrosis	30 minutes discontinued recovered

For patient B there was a suspicion for erythema chronicum migrans. Borrelia serology was negative.

Patient D recovered after 4 days, when doxycycline was replaced by clarithromycin.

Patient E was bitten by a tick in August. Erythema chronicum migrans occurred in September. Doxycycline was given in October.

Patient F recovered within two days after cessation of doxycycline.

Patient G recovered within three weeks of cessation of doxycycline. The patient suffered from similar complaints while using minocycline. Paraesthesia is mentioned in the SmPC of minocycline [6].

Patient H was bitten by a tick and treated with doxycycline for the suspicion of early symptoms of Lyme's disease. The paraesthesia of the limbs occurred independent of sunlight exposure. The patient recovered within eleven days after cessation of doxycycline.

Patient J was diagnosed with Borreliosis (IgG and IgM positive) and suffered from paraesthesia of both hands. No signs of neuroborreliosis were present. After the paraesthesia worsened and became increasingly painful. Doxycycline was withdrawn. The patient recovered within 24- 48 hours.

The reports of patient K, L and M are less supportive of this association, but are listed in the table for the sake of completeness.

Patient K suffered from paraesthesia of the left hand and lower arm only, expanding to oedema of this hand one hour after intake of doxycycline on the second day of antibiotic therapy. Doxycycline was withdrawn, the oedema of the hand has resolved but the paraesthesia still persisted at the moment of reporting.

Patient L suffered from oedema, ulceration and paraesthesia of the second and third finger of the left hand. The patient recovered within two days after cessation of doxycycline, however he was also treated with fusidinic acid.

The reactions and corresponding latency periods for patient M are indicative for an allergic reaction. The patient was treated with cetirizine, dexamethasone and prednisone. The patient had previously suffered from hypersensitivity while using doxycycline, amoxicillin and erythromycin.

Other sources of information

SmPC

The Dutch SmPC of doxycycline does not mention paraesthesia [1-4]. Paraesthesia is also not described in the US SmPC [7]. However, paraesthesia is mentioned in doxycycline SmPC's from New Zealand [8] and Australia [9].

Literature

Literature on the association between doxycycline and paraesthesia is scarce. In an article by Frost et al. [10] six of 15 patients receiving doxycycline 200 mg initially and 100 mg twice daily for 7 days developed abnormal sunburn and 10 of 15 patients had paresthesias consisting primarily of tingling sensations and burning of exposed body areas including the hands, feet, and nose. Five subjects experienced paresthesias without developing an abnormal sunburn reaction and 5 developed both; 1 developed an abnormal sunburn reaction but no paresthesias.

Databases

On January 11th 2013 the database of the Netherlands Pharmacovigilance Centre Lareb contained 13 reports of Preferred Term (PT) Paraesthesia associated with the use of doxycycline, which was not reported disproportionately (ROR = 1.0, 95% CI 0.6 – 1.8). 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: 13	1.0 (0.6 – 1.8)
	WHO: 216	1.3 (1.1 – 1.4)
	EMA: 30	1.5 (1.0 – 2.1)

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 [11].

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

Mechanism

No information was found on a possible mechanism for paraesthesia caused by doxycycline.

Discussion and conclusion

The association between doxycycline and paraesthesia has been reported to Lareb 13 times, although three cases are not supportive for this association. For the other ten cases, a positive dechallenge was reported five times.

Although the Reporting Odds Ratio (ROR) of this association is not statistically significant in the Lareb database, it is supported by a statistically significant disproportionality in the WHO- and Eudravigilance database. The association is also described in SmPC's from Australia and New Zealand [8,9].

Lymes's disease itself can cause peripheral nerve disorders. By definition, nervous system involvement only occurs in disseminated Lyme disease. Specific syndromes tend to be divided into those with fairly abrupt onset and dramatic presentations (eg, meningitis, facial

nerve palsy, radiculoneuritis, focal encephalitis) and those with more indolent onset and protracted courses (eg, diffuse polyneuropathy). Acute neurologic involvement usually occurs weeks to several months after the tick bite and may be the first manifestation of Lyme disease [12].

In the cases reported to Lareb doxycycline was used six times for the (prophylactic) treatment of Lyme disease, although for patient B Borrelia serology was negative. Peripheral nerve disorders would not be expected to occur shortly after the tick bite. When taking into account the time between the tick bite, start of doxycycline and reported latency period, only in patient E the paraesthesia could possibly be a manifestation of neurologic involvement of Lyme disease.

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]. Most patients who experienced paraesthesia used doxycycline for (prevention of) Lyme's disease, where a higher dosage per day is indicated than for other infections. Although in the Lareb cases the prescribed daily dose is not available for some cases, only the strength of the doxycycline tablets used. The fact that most patients used doxycycline for Lyme disease possibly indicates that the paraesthesia is a dosage dependent effect.

Although confounding by Lyme disease itself cannot be ruled out entirely, the cases Lareb received, supported by WHO- and Eudravigilance data, suggest that doxycycline might have a causative role in the occurrence of paraesthesia.

- Signal of paraesthesia associated with the use of doxycycline

References

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