

1.1. Doxycycline and smell and taste disorders

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* [1,2]. In the Netherlands, 947,790 persons used doxycycline in 2007 [3].

Ageusia is the complete or severe loss of the subjective sense of taste. Dysgeusia is a condition characterized by alterations of the sense of taste which may range from mild to severe, including gross distortions of taste quality [4].

Anosmia and parosmia is the loss of or impaired ability to smell [4].

This report studies the association between doxycycline and ageusia/dysgeusia and anosmia/parosmia.

When a taste disturbance is reported, it is likely that an impaired ability to smell is the reason for reporting, since altered smell sensation greatly influences the taste perception. However since it is not sure if this is true for all the patients in the reports, it has been chosen to use the coding as reported by the reporter.

Reports

Until March 18, 2009, the Netherlands Pharmacovigilance Centre Lareb received 36 reports on smell and taste disorders in association with the use of doxycycline. In these reports ageusia was coded if the reporter reported taste loss, and anosmia was coded if the reporter reported loss of smell. The reported latency varied from hours to 17 days. In one report recovery was reported, in the other reports the patient had not recovered at the time of reporting or the outcome was not reported. Twenty-nine of the reports concerned women, and ages ranged from 33 to 82 years. In ten of the reports both smell and taste disorders were reported.

Table 1. Reports of smell and taste disorder 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, 35821, F, 77	doxycycline 100 mg, Lyme's disease		parosmia, taste loss	not reported, discontinued, not recovered
B, 55390, M, 61	doxycycline 100 mg, Lyme's disease	meloxicam, glucoseamine	taste loss	17 days, discontinued, unknown
C, 68696, F 69	doxycycline 100mg, Lyme's disease	carbasalate calcium, fosinopril/hydrochlorothiazide, multivitamins, oxazepam, simvastatin	mouth irritation, taste loss, throat pain	2 days, drug withdrawn, unknown
D, 10256, F	doxycycline 100mg	bromhexine syrup	parosmia, taste loss	not reported. unknown, not reported
E, 11716, F, 48	doxycycline 100 mg, acute nasopharyngitis		parosmia, taste loss	days, no change, not reported
F, 13232, F, 64	doxycycline 100mg, acute sinusitis		taste metallic	minutes, no change, not reported

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
G, 15351, F, 47	doxycycline 100 mg		taste alteration, tongue black	10 days, not reported, not reported
H, 18057, F, 45	doxycycline 100 mg	budesonide nasal spray	paraesthesia mouth, taste perversion	2 days, drug withdrawn, not reported
I, 18286, M, 57	doxycycline 100 mg		taste loss	not reported, drug withdrawn, not reported
J, 20732, F, 73	doxycycline 100 mg	levothyroxine	taste perversion, tongue discolouration	2 days, drug withdrawn, not reported
K, 23610, M, 38	doxycycline 100 mg, upper respiratory tract infection		parosmia, taste loss	not reported, no change, not reported
L, 24855, F, 35	doxycycline 100 mg	loratadine, ethinylestradiol/levonorgestrel	taste metallic, tongue black	7 days, drug withdrawn, not reported
M, 25316, F, 56	doxycycline 100 mg, prednisolone 5 mg upper respiratory tract infection,	zopiclon	anosmia	1 day, drug withdrawn, not reported
N, 26987, F, 53	doxycycline 100 mg, metronidazole 500 mg	atenolol, hydrochlorothiazide	burning feeling vagina, cheilitis, taste perversion	not reported, unknown, not reported
O, 28971, M, 50	doxycycline 100 mg, acute sinusitis	paracetamol	dysosmia	not reported, drug withdrawn, not reported
P, 30369, F, 52	doxycycline 100 mg upper respiratory tract infection		parosmia	3 days, drug withdrawn, not yet recovered
Q, 31462, F, 61	doxycycline 100 mg chronic obstructive pulmonary disease	acetylcysteine, calcium carbonate, alendronate, prednisolone	anosmia	1 day, discontinued, not recovered
R, 38007, F,	doxycycline 100 mg, acute bronchitis		parosmia	10 days, discontinued, not recovered
S, 38008, F,	doxycycline 100 mg, acute bronchitis	furosemide, omeprazole, prednisolone, levothyroxine, xylometazoline nasal spray	parosmia	10 days, discontinued, not recovered
T, 40320, F,	doxycycline 100 mg, acute sinusitis		anosmia, taste bitter	days, drug withdrawn, not recovered
U, 41540, F	doxycycline 100 mg	diazepam, ethinylestradiol/levonorgestrel, bromocriptine	taste loss	2 days, drug withdrawn, not recovered
V, 45486, M, 62	doxycycline 100 mg, unspecified otitis media		anosmia	hours, drug withdrawn, not recovered

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
X, 51970, F, 47	doxycycline 100 mg, bronchitis		parosmia, taste loss	1 week, not applicable, not recovered
Y, 53594, F, 82	doxycycline 100 mg, malaise	losartan/ hydrochlorothiazide	dysgeusia	7 days, no change, not recovered
Z, 57432, F, 66	doxycycline 100 mg, sinusitis	ibuprofen	Raynaud's syndrome, skin chaped, taste loss, vasovagal reaction	days, no change, recovering
AA, 66244, F, 75	ciprofloxacin 500 mg, doxycycline 100 mg	sumatriptan, metoprolol	taste loss	7 days, no change, not recovered
AB, 73745, F, 43	doxycycline 100 mg, infection	alphacalcidol, simvastatin	taste loss	1 day, no change, not recovered
AC, 76094, F, 33	doxycycline 100 mg, infection		taste loss	1 day, no change, not recovered
AD, 76650, F, 34	doxycycline 100 mg, sinusitis		anosmia, taste loss	not reported, unknown, not recovered
AE, 77424, F, 61	doxycycline 100 mg, sinusitis	acetylsalicylic acid, levothyroxine, atorvastatin, estradiol vaginal cream	ageusia, anosmia	3 days, no change, not recovered
AF, 77650, M, 59	doxycycline 100 mg, respiratory tract infection	levothyroxine	ageusia, anosmia	8 days, not applicable, recovered
AG, 83519, M, 44	doxycycline 100 mg, bronchitis	formoterol/ budesonide inhalation	facial swelling, anal pain, mouth irritation, taste loss, exanthema	2 days, drug withdrawn, not recovered
AH, 83899, F, 63	doxycycline 100 mg, cough	salmeterol/fluticas on inhalation., codeine	taste metallic	9 days, drug withdrawn, not recovered
AI, 295, F	doxycycline 100 mg, unspecified	metronidazol 500 mg	malaise, stomatitis, taste perversion	2 days, no change, not reported
AJ, 2159, F	doxycycline 100 mg, unspecified	budesonide nasal spray	fatigue, taste perversion	1 day, unknown, not reported
AK, 5416, F	doxycycline 100 mg	piroxicam, paracetamol, ethinylestradiol/le vonorgestrel, xylometazoline nasal spray	parosmia, taste loss	2 days, drug withdrawn, not reported

Other sources of information

Literature

A Pubmed search using the following MeSH terms "Doxycycline", "Ageusia", "Dysgeusia", "Olfaction Disorders" yielded one case report in which a male developed anosmia while using doxycycline for a skin disorder [5]. In a general review about drug induced smell and taste disorders doxycycline is mentioned as a possible cause of smell disorders [6].

Databases

On March 18, 2009 the Netherlands Pharmacovigilance Centre Lareb had received 36 reports on smell and taste disorders in association with doxycycline use, see Table 1 for detailed information. The Reporting Odds Ratios in the Lareb database and the WHO database are presented in Tables 2 and 3. The number of total reports in Table 2 exceeds 36 because in 10 reports both smell and taste disorders are reported.

Since smell- and taste disorders are rarely considered to be serious according to the CIOMS criteria, data from the Eudravigilance database are not provided for this association..

Table 2. ROR of the associations between doxycycline and smell and taste disorders in the Lareb database.

Reaction	Number of reports	ROR (95% CI)
Ageusia	18	3.6 [2.2-5.8]
Dysgeusia	11	1.5 [0.82-2.7]
Anosmia	7	6.6 [3.1-14.2]
Parosmia	10	7.6 [4.0-14.6]

Table 3. ROR of the associations between doxycycline and smell and taste disorders in the WHO database.

Reaction	Number of reports	ROR (95% CI)
Taste perversion	40	0.76 [0.55-1.0]
Taste loss	43	2.6 [1.9-3.5]
Parosmia	58	4.9 [3.8-6.4]

Mechanism

Antibiotics can induce abnormalities of both taste and smell. However reports of taste loss or distortion are more common than smell loss. Doxycycline induced taste disorders can also be explained through the pharmacodynamic of this drug.

Antibiotics can alter the normal oral, gastric and intestinal flora which can lead to superimposed infections (e.g. candidiasis, caries) and periodontal disease that can influence taste function adversely [7].

Other than the above mentioned explanation for doxycycline induced smell- and taste disorders, the exact mechanism is unclear, however these drugs can reduce the ability of bacteria to adhere to epithelial cells *in vitro*. By analogy, these drugs may interfere with binding of tastants and odorants to their specific receptor [6]. Some anti-bacterials taste bitter, metallic and/or sour at concentrations that occur in salivary secretion, implying a direct influence of the taste system [7].

Discussion and Conclusion

Doxycycline is commonly used in the treatment of upper respiratory tract infection. The infection itself could also cause reduction in smell and taste. In a spontaneous reporting system a pharmacovigilance centre is dependent on reports made of ADRs. Even though there is a possibility of confounding by indication, 36 reports of smell and taste disorders, significantly more often reported in the Lareb and WHO database, except for dysgeusia/taste perversion, is indicative for a signal, even though the causality of the individual cases themselves are not. Besides, in three of the reports the indication was Lyme disease which is not associated with smell and taste disorders. Other possible confounding factors include the co-medication. A few patients also used other drugs such as corticosteroids (oral or nasal spray) or metronidazole which are also known to induce smell and taste disorders [7]. Levothyroxine and hypothyroidism are also associated with smell and taste disorders.

The Netherlands Pharmacovigilance Centre Lareb has received 36 reports concerning smell and/or taste disorders related to the use of doxycycline. The majority of the reports concern female patients (n=29). This association is disproportionally present in both the Lareb as well as the WHO database except for dysgeusia/taste perversion. Information about this association in literature is limited to one case report. Possible mechanism for this ADR include interference with binding of tastants and odorants to their specific receptor, alterations of the oral, gastric and intestinal flora which can lead to superimposed infections (e.g. candidiasis, caries) and periodontal disease and the fact some anti-bacterials taste bitter, metallic and/or sour at concentrations that occur in salivary secretion.

References

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This signal has been raised on October 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).