

Kwartaalbericht

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Voorwoord

In dit laatste Kwartaalbericht van 2009 vindt u opnieuw een brede afwisseling van signalen die naar het oordeel van Lareb de aandacht van het College verdienen. Hoewel het in 2009 erg druk geweest is – het aantal meldingen zal dit jaar waarschijnlijk boven de 8500 uitkomen! – is het toch weer gelukt om een aantal signalen verder uit te werken en u te presenteren.

Het bericht '*ACE-inhibitors and nightmares or abnormal dreaming*' is geschreven op uw verzoek en staat ook op de actielijst van de Collegevergadering. Lareb geeft in het bericht de aanwezige informatie en bespreekt deze, maar heeft geen duidelijke conclusie aan u voor te leggen.

Er is de afgelopen periode een wat groter aantal 'short notes' verzameld die in dit kwartaalbericht zijn opgenomen. Het gaat om inconsistenties die we bij ons werk tegenkwamen of administratieve onvolledigheden.

Het spreekt vanzelf dat ook bij Lareb het laatste kwartaal (en ook wel een deel van het derde kwartaal) in het teken van de H1N1-pandemie staat. Lareb heeft zich voorbereid op een groot aantal meldingen en volgt op verzoek van het ministerie van VWS ook een groot cohort gevaccineerden gedurende een aantal maanden. Het spreekt vanzelf dat ook het CBG voortdurend geïnformeerd wordt over de binnengekomen meldingen en bij ernstige meldingen er direct contact opgenomen wordt. Gezien de onrust rond deze pandemie is goede communicatie tussen alle betrokkenen in de geneesmiddelketen van groot belang – met respect voor ieders taak en positie.

Kees van Grootheest,
directeur Lareb

1. Observations

1.1. Proton pump inhibitors and tongue discolouration

Introduction

Proton pump inhibitors (PPIs) are widely used for the treatment of oesophageal reflux disease, treatment and prophylaxis of (NSAID-associated) duodenal and benign gastric ulcers and relief of dyspeptic symptoms [1-5]. The PPIs available in the Netherlands are: esomeprazole (Nexium®), lansoprazole (Prezal®), omeprazole (Losec®), pantoprazole (Pantozol®) and rabeprazole (Pariet®). Their mechanism of action is based on inhibition of the hydrogen-potassium adenosine triphosphatase enzyme system (the 'proton pump') in the gastric parietal cells, which is the final stage in the production of gastric acid in the stomach. The inhibition is dose dependent and affects both basal and stimulated acid secretion [1-5].

Tongue discolouration is an, often harmless, abnormal colour change of the tongue. It can be caused by an altered oral microbial growth. Tongue discolouration is not mentioned as possible adverse drug reaction in the SmPCs of PPIs [1-5]. Here, the reports received by the Netherlands Pharmacovigilance Centre Lareb concerning tongue discolouration associated with the use of PPIs will be discussed.

Reports

On July 14, 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained eight reports (Table 1) concerning tongue discolouration in association with the use of a proton pump inhibitor. In two of these patients a black (hairy) tongue was reported with concomitant use of omeprazole and an antibiotic. As a black (hairy) tongue is a well known ADR of antibiotics these reports are not mentioned in Table 1.

Table 1. Reports of tongue discolouration associated with the use of proton pump inhibitors.

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 77525 F, 6	omeprazole (Losec® mups)		tongue discoloration (yellow)	days discontinued recovered + rechallenge
B 84060 F, 44	omeprazole (omeprazole actavis) prophylaxis	ibuprofen	tongue discoloration (black)	2 days discontinued recovered a week after discontinuation
C 25222 M, 28	pantoprazole (Pantozol®)		tooth disorder saliva increased bitter taste white tongue	not reported discontinued recovering
D 32230 F, 78	omeprazole (Losec® mups)	acetylsalicylic acid oxazepam	tongue discolouration (orange) dry mouth taste perversion	22 months discontinued recovering

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
E 19497 F, 75	omeprazole (Losec® capsule)	colestyramine mogadon simvastatin loratadine beclometasone (nasal)	taste alteration malaise vomiting tongue discolouration (red/black)	2 days discontinued not reported
F 48484 M, 16	omeprazole pantoprazole (Pantozol®)	nifedipine	tongue discolouration (orange)	4 months discontinued not recovered (tongue discolouration started during omeprazole used and continued when substituted to pantoprazole)

Two patients (A, B) recovered after withdrawal of the drug. The other four patients (C, D, E, F) were not recovered or were recovering at time of reporting. A positive rechallenge was reported in one patient (A). The reported colour of the tongue varied: red/black (E), white (C), yellow (A) and black (B) were reported once and an orange discolouration of the tongue was reported twice (D, E). Patient D takes the drug in the evening; the discolouration of the tongue diminishes during the day. The time between start of the drug and discolouration of the tongue varied from two days to almost two years.

Other sources of information

SmPC

None of the PPI SmPCs mentions tongue discoloration as possible adverse drug reaction [1-5].

Literature

Tongue discolouration has been associated with the use of PPIs as eradication therapy combined with antibiotics [6]. None of the proton pump inhibitors has been associated with tongue discolouration when used as single therapy before.

Databases

On July 14, 2009, reports of PPIs and tongue discoloration were disproportionately present in both the Lareb and the WHO database (Table 2). Although it must be taken into account that of the WHO-cases 24 patients used antibiotics concomitantly (1x lansoprazole, 9x omeprazole, 2x pantoprazole, 1x esomeprazole, 1x rabeprazole).

Table 2. The reporting odds ratios of PPIs and tongue discolouration in the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Drug and ADR	Number of reports	ROR (95% CI)
PPI and tongue discolouration	Lareb: 6	2.4 (1.1-5.5)
	WHO (omeprazole): 40	3.1 (2.3-4.3)
	WHO (pantoprazole): 8	3.4 (1.7-6.7)
	WHO (esomeprazole): 12	2.2 (3.8-6.7)
	WHO (lansoprazole): 22	3.8 (5.7-8.7)
	WHO (rabeprazole): 5	1.3 (3.2-7.8)

Prescription data

The increasing number of patients using PPIs in the Netherlands is shown in Table 3.

Table 3. Number of PPI users in the Netherlands between 2005 and 2008 [7]

Drug	2005	2006	2007	2008
omeprazole	762,460	895,440	1,026,000	1,260,000
pantoprazole	413,640	458,260	504,250	575,570
lansoprazole	28,096	26,712	23,700	23,489
rabeprazole	67,276	70,748	68,749	77,624
esomeprazole	225,350	256,730	280,900	325,090
Total	1,496,822	1,707,890	1,903,599	1,936,683

Mechanism

The decreased gastric acid production caused by PPIs leads to an increased pH in the stomach and in the oral saliva [8]. An increased oral pH could affect oral microbial growth [9]. PPIs can also influence oral microbial growth by causing a decreased saliva production [1-5]. Alterations in oral microbial flora can lead to tongue discolouration. Overgrowth of chromogene micro-organisms on the tongue papillae and colorings can be responsible for discolouration of the tongue [11]. Another possible explanation is the use of red, black and yellow ferric oxide (E172) in Losec® capsules and MUPS, Pantozol® tablets, Prezal® capsules, Pariet® tablets and Nexium® tablets [1-5,10], although no supportive literature for this possible mechanism was found. Patient A, C, D, E and F in Table 1 used one of these formulations.

Discussion

PPIs can probably induce tongue discolouration due to their ability to decrease saliva production and increase the pH of the oral mucosa and therefore cause an altered microbial flora. Six cases of tongue discoloration were reported in association with PPIs, including one patient with a positive rechallenge. No supportive case reports for this association were found. This association was disproportionately present in both the Lareb and the WHO database.

Not all patients were recovered after withdrawal of the drug at time of reporting to Lareb, which could be explained by the fact that recovery of oral microbial flora can take weeks to months [10]. Possible other causes for this adverse event could be the use of red, black and yellow ferric oxide (colour) in the formulations and, for example, cigarette smoke and alcohol use [10,12].

The time to onset was a couple of days in four patients (A, B, C, E) and respectively four and 22 months in patients D and F. This could indicate that two

different mechanisms for PPI induced tongue discolouration exist: altered microbial flora and discolouration by the colourant used in the capsule or tablet.

Conclusion

Tongue discolouration should be added as possible adverse drug reaction in the SmPCs of all proton pump inhibitors.

- Tongue discolouration should be added in the SmPC's of all proton pump inhibitors.

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1.2. 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 gastro-intestinal 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 changed, not reported

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
F, 13232, F, 64	doxycycline 100mg, acute sinusitis		taste metallic	minutes, no change, not reported
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

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
V, 45486, M, 62	doxycycline 100 mg, unspecified otitis media		anosmia	hours, drug withdrawn, not recovered
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 chapped, 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/fluticasone inhalation, codeine	taste metallic	9 days, drug withdrawn, not recovered
AI, 295, F	doxycycline 100 mg, unspecified	metronidazole 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/levonorgestrel, 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 disproportionately 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.

- Smell and taste disorders should be included in the SPC of doxycycline containing oral preparations

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1.3. Tamsulosin and epistaxis

Introduction

Tamsulosin (Omnic[®]) is an α 1-receptor antagonist and is indicated for the *treatment of lower urinary tract symptoms (LUTS) related to benign prostate hyperplasia (BPH)*. In 2008, the number of patients using tamsulosin was about 165,320 [1]. A frequent Adverse Drug Reaction (ADR) of tamsulosin is dizziness [2]. Epistaxis, or nose bleed, is estimated to occur in 60% of persons during their lifetime with a higher incidence during the winter months. The prevalence is increased for children less than 10 years of age, is lower for adolescents and young adults and then rises again after the age of 35 years. Nose bleeds are more common in older patients; a mean age of 64 is mentioned [3]. Among hospitalized patient with nose bleeds, male patient are more presented in the age of 20-49 years. From the age of 50, no sex differences were found [4]. Approximately 6% of the patients with nosebleeds seek medical treatment. More than 90% of episodes of epistaxis occur along the anterior nasal septum, at a site called Kiesselbach's area [3]. Epistaxis is not mentioned in the SmPC of tamsulosin [2].

This report describes the occurrence of epistaxis with the use of tamsulosin.

Reports

Up to July 7, 2009, Lareb received eight moderately documented reports of epistaxis associated with the use of tamsulosin (see Table 1).

Latency time varied from 1 day to 1 year and is mostly within a few months after start. Patient G also mentioned nose dryness and patient A also mentioned tinnitus as other ADRs. Three patients (A, D and E) did not use any concomitant medication.

The outcome was reported in five patients. In one of these reports (patient H), frequency of the bleedings reduced after tamsulosin was replaced by alfuzosin. This patient also had a medical history of xylometazolin abuse and nose bleeding which required electric cautery.

Three patients (B, C, D) recovered (with sequel for patient D) on ongoing therapy with tamsulosin. For patient A, the action with the drug is not known. Patient E visited an ear, nose and throat specialist, who diagnosed an inflammation of the upper blood vessel of the nose. After electric cautery, the patient recovered. Patient C and F used acenocoumarol and beclometasone as concomitant medication, which can induce epistaxis. Patient H used metoprolol, which has rhinitis as well known ADR due to its vasodilatation effects.

Table 1. Reports of epistaxis with the use of tamsulosin.

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 56008 M, 60	tamsulosin 0.4mg 1dd benign prostatic hyperplasia		epistaxis tinnitus	3 months, March action unknown recovered
B 75117 M, 56	tamsulosin 0.4mg 1dd prostatic hypertrophy	escitalopram	epistaxis	2 days, February no change recovered
C 83555 M, 73	tamsulosin 0.4mg 1dd benign prostatic hyperplasia	acenocoumarol verapamil digoxin	epistaxis	within the same month, May no change recovered
D 82420 M, 61	tamsulosin 0.4mg 1dd benign prostatic hyperplasia, ciprofloxacin prophylaxis for biopsy		epistaxis	1 year (tamsulosin), 3 days (ciprofloxacin), November Ciprofloxacin withdrawn, tamsulosin ongoing recovered with sequel
E 31672 M, 64	tamsulosin 0.4mg 1dd		nosebleed	3 weeks, April no change unknown
F 22177 M, 77	tamsulosin 0.4 1dd hyperplasia of prostate	salmeterol nitrazepam beclometasone (nasal) ketokonazole	epistaxis	1 day, October discontinued not reported
G 14030 M, 59	tamsulosin 0.4 mg 1dd	doxycyclin heparinoid creme amoxicillin/ clavulanic acid	nosebleed, nose dryness	2 days, May drug withdrawn before the event occurred. not reported
H 48827 M, 69	tamsulosin 0.4mg 1dd dutasteride 0.5mg 1dd	doxazosin enalapril/ hydrochloro- thiazide metoprolol	epistaxis	6 weeks, November tamsulosin replaced by alfuzosin. frequency bleedings reduced

Other sources of information

Literature

Epistaxis is not mentioned in the SmPC of tamsulosin. Other symptoms which can manifest itself in the form of epistaxis, such as thrombocytopenia, are also not mentioned. Rhinitis, a risk factor for epistaxis, is a well known ADR [2].

The SmPC of terazosin, another α 1-antagonist (brand name, Hytrin®), does not mention epistaxis [5]. However, the SmPC of terazosin generic mentions epistaxis as an ADR seen in clinical setting with an unknown causal relationship [6]. In this SmPC, thrombocytopenia is also mentioned as ADR seen in post marketing setting [6]. In literature, we found no cases of epistaxis with the use of tamsulosin or α -blockers.

Databases

In the Lareb database the association between tamsulosin and epistaxis is disproportionally present. On July 7, 2009, the Lareb database contained eight reports of epistaxis and tamsulosin, with an odds ratio of 4.8 (95% CI 1.9 - 6.7). In the database of the World Health organization (WHO) there were 17 reports of epistaxis with the use of tamsulosin with an odds ratio of 1.6 (95% CI 0.96 - 2.5). On July 24, 2009, the Eudravigilance database - that contains mainly reports of serious ADRs - contained 15 reports of tamsulosin associated epistaxis. Thirteen were rated serious, of which ten due to hospital admission, two due to disability and one due to other non-specified reasons. Thrombocytopenia was reported once, atrial fibrillation - without mention of coumarine use - three times. In six cases a drug interaction was reported. All 15 patients were of male sex, ages ranging from 39 to 75 years.

Mechanism

Alpha-1-agonists such as xylometazolin or oxymetazolin cause decongestion of the nose due to vasoconstriction, and these drugs are indicated for treatment of epistaxis [3]. Alpha-1-receptor antagonists, like tamsulosin, cause vasodilatation [7]. Hypothetically, vasodilatation increases the risk of nose bleeds. Additionally, vasodilatation of the nose also leads to swelling of the mucosa and nose congestion. Swelling of the mucosa and nose congestion can lead to rhinitis, a well known side effect of tamsulosin. Rhinitis is a risk factor for the occurrence of epistaxis [3].

Discussion and conclusion

There are several factors associated with nose bleeds. These include rhino sinusitis, systemic conditions associated with coagulopathy, septal perforations, dry mucosa and neoplasm [3]. Of the eight reports Lareb received, three patients had additional factors such as nasal dryness, the use of acenocoumarol or nasal corticosteroids and the concomitant use of antibiotics. Another patient received antihypertensive drugs as concomitant medication. Hypertension may also contribute to epistaxis, although this theory is controversial [3].

There is an increased incidence of nose bleeds during winter months, probably due to dehumidification of the nasal mucosa [3]. However, since only two of the eight reports concern patients who experienced epistaxis in the winter months (December to March) this cannot be the explanation in all cases. Remarkably, all reports concerned males while no sex difference was found after the age of 50 in literature [4].

Although other factors for nose bleeds cannot fully be excluded, the number of the reports and the pharmacological properties of tamsulosin supports the relation between epistaxis and tamsulosin. The association between epistaxis and tamsulosin is disproportionally present in the Lareb database. For another α 1-antagonist, terazosine, epistaxis is described in the SmPC. Epistaxis should be mentioned in the SmPCs of all tamsulosin containing products.

- Epistaxis should be mentioned in the SmPC of tamsulosin
- A discrepancy for mentioning epistaxis between the SmPCs of terazosin brand and terazosin generic was found

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1.4. Oseltamivir and coumarin potentiation

Introduction

Oseltamivir (Tamflu[®]) is a neuraminidase inhibitor indicated for use in early phases of influenza illness or for prophylactic use in this disease [1]. Oseltamivir is a pro-drug which eventually exerts its clinical effect by selective inhibition of neuraminidase which is essential for influenza virus replication. Given recent recommendations for oseltamivir use in H1N1 novel type I influenza a marked increase in its use can be expected in novel outbreaks of this infection.

Acenocoumarol and phenprocoumon (Marcoumar[®]) are coumarin derivatives registered for *prophylactic use to reduce thromboembolic events*. Both drugs act as vitamin-K antagonists (VKA), leading to inhibition of coagulation factor II, VII, IX and X synthesis [2,3]. VKAs have a narrow therapeutic range and are substrate of many drug interactions. Low concentrations lead to insufficient thromboembolic risk reduction whereas high serum levels may result in life-threatening bleeding. In 2008 approximately 350,000 patients used acenocoumarol or phenprocoumon in the Netherlands [4]. Internationally, warfarin is more commonly used.

In this report, two cases with significant increases in international normalised ratio (INR) in patients using oseltamivir for prophylaxis are presented. Furthermore an overview of reports in the Eudravigilance and WHO-UMC databases will be provided.

Reports

On September 15, 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports of marked increases in INR.

Report A, presented by a pharmacist, concerns a 54-year-old female who used phenprocoumon for an unspecified indication. Concomitantly used medication consisted of levothyroxine, inhaled salmeterole and fluticasone, vitamin B12, calcium, Vitamin D3 and vitamin B12. Days after start of oseltamivir for prophylactic use, INR rose from 3.5 to 14.0. Withdrawal led to recovery. No information on vitamin K administration or phenprocoumon dose adjustment was provided.

The patient in case B, reported by a hospital pharmacist, is an 82-year-old female with atrial fibrillation and a suspected M. Parkinson. No signs of an active infection were present. Acenocoumarol was used over a year leading to stable anticoagulation. No changes in drug use were performed over an unspecified prolonged period. Three days after oseltamivir use for influenza prophylaxis, INR rose to over 15. Withdrawal of acenocoumarol and vitamin K administration led to recovery. No information of duration of oseltamivir use was provided. Co-medication consisted of spironolactone, digoxin, furosemide, levodopa/carbidopa, folic acid and silver sulfadiazine for topical use.

Table 1. Cases of possible coumarin interactions associated with oseltamivir use reported to Lareb.

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 42969 F, 54 years	oseltamivir prophylaxis phenprocoumon atrial fibrillation	fluticasone fluticasone/ salmeterole hydrochloro- thiazide hydrocobalamin levothyroxine	coagulation time increased (INR 14 from 3.5 before oseltamivir start)	days, withdrawn, no information on phenprocoumon dose adjustment or vitamin K administration recovered
B, 56482 F, 82 years	oseltamivir prophylaxis acenocoumarol atrial fibrillation	spironolactone, levodopa/ carbidopa digoxin furosemide lactulose folic acid dermal silver sulfadiazine	INR increased to >15 in stable patient	days, one year of coumarin use vitamin K administration, dose adjustment no indications for an active infection, no recent modifications in concomitant medication.

Other sources of information

SmPC

The possibility of oseltamivir-coumarin interactions is not addressed in the SmPCs of the products involved [1-3].

Literature

To the best of our knowledge, no case reports or further information is published in peer-reviewed medical journals. However both the Canadian (2006) and British (September 2009) regulatory agencies have issued signals addressing the possibility of coumarin interactions associated with use of oseltamivir [5,6]. Neither of these two reports claim to be conclusive, because of lack of mechanisms known to cause oseltamivir coumarine interactions and potential reporting bias.

Databases

Given the limited number of reports in the database of the Netherlands Pharmacovigilance Centre Lareb, disproportionality could not be assessed.

The database of the World Health Organization (WHO) contained 37 reports of increased PT or INR associated with oseltamivir use (ROR 5.8). A decreased anticoagulatory effect after oseltamivir use was reported four times.

On the 15th of September 2009, the Eudravigilance database contained 42 reports of increased PT or INRs, all rated serious. (Proportionate risk ratio 5.2, CI= 3.8-7.1). No cases of decrease of coumarin effects were reported. Ten cases were poorly documented, lacking essential clinical information and these cases will not be taken into account. Of the remaining 32 better documented cases, clinical significance was the most common reason for rating the reports as serious cases. Decease of patient and disability were both reported once. Life threatening aspects were indicated four times, hospital admission or prolongation of a stay in hospital were reported three times. Reactions occurred both in prophylactic setting (n=13) and therapeutic use (n=13). In six reports no information on

indication was provided. Eleven cases of significant increases (INR>6 occurred in both groups), were reported. In an additional three cases INR increased to just below six. In one case, no INR was specified. However in this report a fourfold increase was mentioned.

In Eudravigilance, eleven reports concerned minor increases (INR increase less than two). Information on co medication is limited. Twenty-one patients were aged more than eighty years.

Mechanism

The mechanism for coumarin potentiation by oseltamivir is unclear. No effects of oseltamivir on the Cytochrome P-450 enzyme system, which could explain effects on coumarin metabolism, are known [8]. Excretion occurs predominantly renal in all drugs involved, although to a different extent.

Discussion and conclusion

This signal is based on two cases presented to the Netherland's Pharmacovigilance Centre Lareb of marked INR increases, leading to a substantial risk for potentially life-threatening bleeding. Internationally 42 cases were presented to the Eudravigilance, while the WHO-UMC database contains 37 reports. In both databases these numbers lead to a marked disproportionality. Signals concerning this association were issued by the Canadian and British regulatory agencies.

Although the number of Dutch reports is limited, the reports are remarkable because the reaction occurred in prophylactic setting and because of the clinical significance of the reported INR increases.

The number of reports in the international databases, its disproportionality and especially the thirteen cases that occurred in a prophylactic setting may support an association between oseltamivir use and coumarine potentiation. However causality assessment on these reports is hampered by the following factors leaving significant space for biases affecting the association of this report. First, it must be noticed that the international cases, concern an older population, 21 patients were older than 80 years at the time of INR increases. Unfortunately, no information was provided on anticoagulatory history or previous INR values. Furthermore, information on concomitant medication is limited and not always in line with reported co morbidity. Ciprofloxacin, for which cases of coumarine potentiation are known [7], was used by one patient (INR increased to 4.8). Besides effects of this drug, also the infection for which it was used could have been causative for the increased INR.

With respect to the Canadian signal , it must be noticed that a significant number of the Canadian reports (eleven of a total nineteen reports) originated from a single source.

However, given the cases presented in this quarterly report and the issued signals from British and Canadian regulatory agencies, an interaction cannot be excluded and attention for the possibility of an oseltamivir-induced coumarin potentiation is especially warranted in the present setting of expected increases in oseltamivir use.

- Signal of possible oseltamivir induced coumarin potentiation through unknown mechanism.
- Discussion in international setting is warranted

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2. Reports on request of the MEB

2.1. ACE-inhibitors and nightmares or abnormal dreaming

Introduction

In a previous quarterly report (2009-2) the association between AT₁ receptor antagonists and nightmares or abnormal dreaming was described. The current report describes nightmares (paroniria) or abnormal dreaming associated with the use of ACE-inhibitors and is made on request by the Medicines Evaluation Board. Angiotensin-converting enzyme (ACE) inhibitors are widely used for the treatment of *hypertension and heart failure*. The following ACE-inhibitors are registered in the Netherlands: benazepril (Cibacen[®]), capropril, cilazapril (Vascase[®]), enalapril (Renitec[®]), fosinopril (Newace[®]), lisinopril (Zestril[®]), perindopril (Coversyl[®]), quinapril (Acupril[®]), ramipril (Tritace[®]),trandolapril (Gopten[®]) and zofenopril (Zofil[®]). Most ACE-inhibitors are also registered in combination with other antihypertensive drugs.

A nightmare is defined by the DSM IV criteria as a frightened dream. Clinically the most common definition for nightmare is an unpleasant or frightening dream occurring in REM sleep [1].

The SmPC of enalapril mentions abnormal dreaming as a possible adverse drug reaction [2]. The SmPCs of the other ACE-inhibitors do not mention nightmares or abnormal dreams [3-12]. Most SmPCs do mention sleep disturbances or insomnia [2,3,6-12].

Reports

On October 22, 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained nine reports (Table 1) concerning nightmares or abnormal dreaming during the use of ACE-inhibitors. Five reports concerned enalapril, three reports captopril and one perindopril. There were no reports of nightmares or abnormal dreaming associated with the other ACE-inhibitors or ACE-inhibitors used in a combination product with other antihypertensive drugs.

Table 1. Reports of nightmares or abnormal dreaming associated with the use of ACE-inhibitors.

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 63740 F, 51	enalapril 5mg hypertension		abnormal dreaming, twitching	3 days discontinued recovered + rechallenge
B 29487 M, 61	captopril 12.5mg	budesonide, formoterol	paroniria	not reported discontinued recovered + rechallenge
C 65153 M, 67	captopril 50mg		nightmares	3 weeks discontinued recovered
D 64270 F, 40	enalapril 5mg hypertension	atenolol/ chlorothalidone	restless sleep, abnormal dreaming	not reported discontinued recovered no adverse reaction when using captopril

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E 7636 F, 54	enalapril 10mg		paroniria	2 days not reported not reported
F 15597 F, 37	enalapril 5mg primary hypertension		nightmares	3 hours no change not reported
G 38431 F, 49	captopril 25mg primary hypertension	ethinylestradiol/ levonorgestrel beclometasone	headache, excessive dreaming	5 months no change not reported
H 91177 F, 44	perindopril 2mg hypertenstion	pantoprazole simvastatin	vision decreased, dreaming abnormal	2 years no change not reported

Four patients (A, B, C, D) recovered after discontinuation of the ACE-inhibitor. In patients A and B a positive rechallenge was reported. Patient D recovered after withdrawal of enalapril and did not experience any adverse drug reactions after switching to captopril. This patient also used atenolol which has previously been associated with nightmares.

Other sources of information

SmPC

The SmPC of enalapril mentions abnormal dreaming as a possible adverse drug reaction (ADR) [2]. Nightmares or abnormal dreams are not mentioned in the SmPCs of the other ACE-inhibitors [3-12].

Literature

Nightmares or abnormal dreaming were associated with ACE-inhibitors (captopril, enalapril and quinapril) previously in a case report [13] and two review articles [1,14]. No case reports were found for the other ACE-inhibitors.

Databases

On August 31, 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained nine cases of abnormal dreaming or nightmares in association with ACE-inhibitors. The reporting odds ratio (ROR) is not statistically disproportional (ROR=0.71, 95% CI: 0.37-1.4)

The database of the World Health Organization contained 310 reports of abnormal dreaming or nightmares (paroniria) associated with the use of ACE-inhibitors (Table 2). The ROR is only statistically disproportional fortrandolapril (ROR=3.7, 95% CI: 1.5-8.8). The ROR for ACE-inhibitors as a group shows a protective effect for these ADRs (ROR=0.86 95% CI: 0.76-0.96).

Table 2. Number of reports on abnormal dreaming or nightmares (paroniria) associated with ACE-inhibitors and disproportionality in the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO database.

Drug	Number of reports	ROR (95% CI)	Number of reports	ROR (95% CI)
	<i>Lareb database</i>		<i>WHO database</i>	
benazepril				
captopril	3	1.15 [0.37-3.6]	74	1.01 [0.81-1.3]
cilazapril				
enalapril	5	0.62 [0.26-1.5]	103	1.03 [0.85-1.3]
fosinopril				
lisinopril			87	1.05 [0.85-1.3]
perindopril	1	n/a	12	1.31 [0.74-2.3]
quinapril			10	1.14 [0.61-2.1]
ramipril			19	0.84 [0.54-1.3]
trandolapril			5	3.7 [1.5-8.8]
zofenopril				
total	8	0.75 [0.37-1.5]	310	0.86 [0.76-0.96]

Prescription data

The number of patients using ACE-inhibitors has increased over the years. In 2008, ACE-inhibitors were used by 912,508 patients (Table 3).

Table 3. Number of patients using ACE-inhibitors in the Netherlands between 2004 and 2008 [15].

Drug	2004	2005	2006	2007	2008
benazepril	726	601	518	453	402
captopril	70,759	61,976	53,406	44,940	40,988
cilazapril	877	786	785	652	679
enalapril	255,280	257,890	296,950	288,630	320,870
fosinopril	59,872	64,449	67,926	61,049	65,671
lisinopril	128,350	138,630	154,140	157,120	177,480
perindopril	87,776	108,440	147,640	168,410	203,610
quinapril	48,677	46,662	47,113	42,962	41,303
ramipril	43,478	45,746	49,825	49,019	54,862
trandolapril	1,016	874	803	753	669
zofenopril	4,270	4,773	5,265	5,412	5,974
Total	701,081	730,827	824,371	819,400	912,508

Mechanism

Nightmares are related to an increased intensity of REM sleep [14]. Drugs can influence REM sleep directly and indirectly. Drugs may influence REM sleep indirectly by suppression of the total REM sleep, leading to an increased intensity of the remaining REM episodes [16]. Nightmares may also occur when drugs that cause REM sleep rebound are withdrawn [17].

In addition to functions such as controlling systemic blood pressure, angiotensin II has several roles in the brain [18]. It is hypothesized that angiotensin II plays a role in functions such as regulation of emotional responses, brain development and the process of sensory information [19]. Also, angiotensin II seems involved in higher regulatory mechanisms controlling responses to stress and anxiety: antagonism of brain angiotensin II could block angiotensin II induced stress and anxiety in rats [20,21].

One study investigated functional relationships between sleep-active neurons and angiotensin II in rats. They found that intracerebroventricular injection of angiotensin II did not alter total sleep time, but significantly changed the sleep architecture with reduction of REM sleep [22].

Discussion

The Netherlands Pharmacovigilance Centre Lareb received nine reports of abnormal dreaming or nightmares in association with the use of ACE-inhibitors. A positive dechallenge was reported in four patients; two of these patients experienced a positive rechallenge. Animal studies have shown a role for angiotensin in the brain [18]. The association is not supported by disproportionality in the Lareb database.

This quarterly report is written in addition to the report concerning the use of AT₁ receptor antagonists and nightmares or abnormal dreaming. The number of patients using ACE-inhibitors is almost twice as high as the number of patients using AT₁ receptor antagonists [17]. However, Lareb received 16 reports of abnormal dreaming or nightmares associated with the use of AT₁ receptor antagonists and only nine for the ACE-inhibitors. This difference could be due to underreporting, but might also be explained by the difference in lipophilicity of the drugs. AT₁ receptor antagonists have a higher lipophilicity than ACE-inhibitors [23], which makes them more susceptible to pass the blood brain barrier and cause neuropsychiatric adverse drug reactions. Besides, not all ACE-inhibitors have the same lipophilicity [23], for example enalapril has a higher logP than captopril. This could explain why patient D experienced abnormal dreaming when using enalapril and did not experience this adverse drug reaction when using captopril.

Conclusion

Abnormal dreaming is mentioned in the SmPC of enalapril. This possible ADR should also be mentioned in the SmPC of captopril. Based on the possible mechanism for this ADR a class effect for all the ACE-inhibitors can be expected. However, this is not supported by reports received by Lareb nor by the reporting odds ratios of the database of Lareb and the WHO.

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3. Short notes

3.1. Bupropion and maniform symptoms

On March 30, 2009, in the official product information of bupropion (Zyban[®] and Zybantabac[®]) it is mentioned in section 4.4, that bupropion is a central working inhibitor of the reuptake of noradrenaline and dopamine. Neuropsychiatric reactions have been reported, among which psychotic and manic symptoms, especially in patients with a known history of psychiatric illness [1,2]. For more information, the text refers to section 4.8 on adverse drug reactions. Although this section mentions that hallucinations are reported as a rare adverse drug reaction, with a frequency between 1/1000 and 1/100, maniform symptoms are not mentioned in this section. In order to avoid any confusion, the information provided in section 4.4 and section 4.8 should cover the same adverse drug reactions. Also in the SmPCs of the bupropion-GSK, Wellbutin[®] and Elontril[®], maniform symptoms are missing in section 4.8 [3-5].

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3.2. Amoxicillin, amoxicillin/clavunilate and black hairy tongue

On July 22, 2009, the Netherlands Pharmacovigilance Centre Lareb had received 37 reports of a black hairy tongue on amoxicillin, and 28 reports on amoxicillin/clavunilate. The Dutch SmPCs of amoxicillin and amoxicillin/clavunilate are inconsistent with regard to mentioning black (hairy) tongue. Some SmPCs do mention this ADR [1,2], while others do not mention this adverse drug reaction [3-5].¹

Black hairy tongue should be mentioned in all SmPCs of amoxicillin and amoxicillin/clavunilate containing products.

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¹ Not all SmPCs have been checked: references are examples that illustrate inconsistency.

3.3. Citalopram and cough

On June 24, 2009, the Netherlands Pharmacovigilance Centre Lareb had received six reports of cough in association with citalopram. The Dutch SmPCs are inconsistent with regard to mentioning cough as adverse drug reaction. Some SmPCs [1, 2] do not mention cough, while others [3-19] do mention this adverse reaction.

Cough should be mentioned in the SmPCs of all citalopram containing products.

References

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11. Dutch SPC citalopram Stada Arzneimittel AG. (version date: 30-6-2008, access date: 24-6-2009) <http://db.cbg-meb.nl/IB-teksten/h27633.pdf>.
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16. Dutch SPC citalopram Katwijk Farma B.V. (version date: 26-10-2004, access date: 24-6-2009) <http://db.cbg-meb.nl/IB-teksten/h30792.pdf>.
17. Dutch SPC citalopram Ranbaxy UK Ltd. (version date: 7-7-2005, access date: 24-6-2009) <http://db.cbg-meb.nl/IB-teksten/h31086.pdf>.
18. Dutch SPC citalopram Pharmachemie B.V. (version date: 21-5-2008, access date: 24-6-2009) <http://db.cbg-meb.nl/IB-teksten/h31125.pdf>.
19. Dutch SPC citalopram Apotex Europe BV. (version date: 23-6-2008, access date: 24-6-2009) <http://db.cbg-meb.nl/IB-teksten/h34746.pdf>.

3.4. Citalopram and hyponatraemia

On June 25, 2009, the Netherlands Pharmacovigilance Centre Lareb had received 17 reports of hyponatraemia in association with citalopram. The Dutch SmPCs are inconsistent with regard to mentioning hyponatraemia as adverse drug reaction. Some SmPCs [1,2] do not mention hyponatraemia, while others [3-19] do mention this adverse reaction.

Hyponatraemia should be mentioned in the SmPCs of all citalopram containing products.

References

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16. Dutch SPC citalopram Katwijk Farma B.V. (version date: 26-10-2004, access date: 25-6-2009) <http://db.cbg-meb.nl/IB-teksten/h30792.pdf>.
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3.5. Risperidon and sudden death

Until July 8, 2009, Lareb received eight reports of sudden death with the use of risperidon. Sudden death has been described in some of the SmPCs of risperidon [1-3]. Other SmPCs of risperidon do not mention sudden death with the use of risperidon [4-6]. Therefore, sudden death should be mentioned in all SmPCs of risperidon containing products.

References

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6. Dutch SmPC risperidon pelpharma. (version date: 22-8-2008, access date: <http://db.cbg-meb.nl/IB-teksten/h31584.pdf>).

3.6. Ranitidine and diarrhoea

On July 14, 2009, the Netherlands Pharmacovigilance Centre Lareb had received 12 reports of diarrhoea in association with ranitidine. The Dutch SmPCs of oral ranitidine are inconsistent with regard to mentioning diarrhoea as adverse drug reaction. Some SmPCs [1-10] do not mention diarrhoea, while others [11-17] do mention this adverse reaction.

Ranitidine should be mentioned in the SmPCs of all ranitidine containing products for oral use.

References

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