

Kwartaalbericht

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Voorwoord

Met genoegen biedt het Nederlands Bijwerkingen Centrum Lareb het College ter Beoordeling van Geneesmiddelen het derde kwartaalbericht van dit jaar aan.

In dit kwartaalbericht vindt u een bericht over stollingsproblematiek dat een bijzondere achtergrond heeft. Dit bericht is tot stand gekomen dankzij de samenwerking die Lareb al enige jaren heeft met de Federatie Nederlandse Trombosediensten. Deze samenwerking heeft er mede toe geleid dat er speciale aandacht is voor bijwerkingen die met stollingsproblematiek te maken hebben. Daar is alle reden voor, want deze problemen scoren hoog in de resultaten van het HARM-onderzoek naar geneesmiddelgerelateerde problemen die leiden tot ziekenhuisopname.

In de Wetenschappelijke Adviesraad van Lareb is aanbevolen ons zo mogelijk meer te richten op groepen geneesmiddelen of groepen gebruikers, waarvan bekend is dat daar relatief veel geneesmiddelgerelateerde problemen voorkomen.

In dit kwartaalbericht vindt u ook twee berichten die al eerder de aandacht van het College vroegen omdat ze u als 'safety concern' zijn toegestuurd. Het is gebruikelijk dat ze, zo nodig nader uitgewerkt, daarna in het kwartaalbericht opgenomen worden.

Kees van Grootheest

1. Observations

1.1. Fexofenadine and bradycardia

Fexofenadine hydrochloride is a non-sedating H₁ antihistamine. It was registered in the Netherlands in 1997. Fexofenadine is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children aged 12 years or older [1,2]. The past few years, the number of patients using prescribed fexofenadine in the Netherlands has been stable around 150,000 [3].

Fexofenadine is as prescription only drug registered as “Telfast[®]”, but is also available over the counter as “STP-free” [1,2].

The SmPC mentions that patients with a history of or ongoing cardiovascular disease should be warned that antihistamines as a drug class have been associated with tachycardia and palpitations [1,2]. Bradycardia is not mentioned in the SmPC of fexofenadine. However, the Netherlands Pharmacovigilance Centre Lareb received the third serious reports in which the use of fexofenadine was associated with bradycardia. In this report the details on this possible association will be described.

Reports

On June 3, 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports concerning bradycardia during the use of fexofenadine. All three reports were reported as serious.

Patient A (report number 28889) is a 27-year-old male who had been using fexofenadine 120 mg once daily for treatment of allergic rhinitis. He developed an extreme bradycardia for which CPR was needed. No ECG's were made the moment the bradycardia occurred. However, when CPR was started, the QTc interval was within normal range. The patient had a serious post anoxic encephalopathy. This case was reported by a cardiologist.

Patient B (report number 73912) is a 37-year-old female who had been using fexofenadine 120 mg once daily and Sublingual Immunotherapy (SLIT) for the treatment of allergy. She developed peripheral oedema, dyspnoea on exertion, weight increase and bradycardia following administration of both drugs, with an unclear time to onset after start of fexofenadine. The patient was hospitalized and both fexofenadine and SLIT treatment were withdrawn, after which she recovered. The consulting cardiologist confirmed bradycardia. On the ultrasound of abdomen and heart no signs of cardiac failure were found. On a CT scan slight pleural effusion was visible, no signs of pericardial effusion or pulmonary embolism. Cardiac failure was excluded by the consulting cardiologist. This case was reported by an internist/allergist.

Patient C (report number 86460) is a 57-year-old female, who developed bradycardia following administration of fexofenadine 120 mg once daily for allergic rhinitis with a latency of ten days after start. Concomitant medication was not reported. The patient was hospitalized. Fexofenadine was withdrawn. The cardiology report mentioned sinusbradycardia approximately 45-50/min, ECG SR 50/min with an early repolarisation V2-3. The patient gradually recovered within a few days and her heart rate increased to normal values (around 70/min). Although the cardiologist suggested a possible vasovagal reaction, this was considered unlikely by her spouse who, like the patient herself, is a general practitioner and described a slow onset and long duration of the complaints. This is not compatible with a vasovagal reaction.

All three patients had no previous history of cardiac disorders. The absence of a prolonged QTc interval was explicitly mentioned in patients A and C. Possible risk factors for the development of bradycardia were not reported.

Other sources of information

SmPC

The Dutch SmPC of fexofenadine mentions tachycardia and palpitations as possible adverse drug reactions, but does not mention bradycardia. It also states that no significant differences in QTc intervals were observed in seasonal allergic rhinitis patients given fexofenadine hydrochloride up to 240 mg twice daily for two weeks when compared to placebo. Also, no significant change in QTc intervals was observed in healthy subjects given fexofenadine hydrochloride up to 60 mg twice daily for six months, 400 mg twice daily for 6.5 days and 240 mg once daily for one year, when compared to placebo. Fexofenadine at concentrations 32 times greater than the therapeutic concentration in man had no effect on the delayed rectifier K⁺ channel cloned from human heart [1,2].

Literature

According to the literature fexofenadine has little cardiotoxicity [4,5]. No case reports of fexofenadine induced bradycardia were found. The safety of fexofenadine in children aged six to 11 years with seasonal allergic rhinitis has been assessed in a large (n=875), double-blind, randomized, placebo-controlled, parallel study. No statistically significant electrocardiographic effects were discovered [6].

Databases

In June 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of bradycardia in association with fexofenadine. The reporting odds ratio (ROR) is statistically disproportional (ROR = 9.5, 95%CI: 3.0-30).

The database of the World Health Organization (WHO) contained eight reports of bradycardia during the use of fexofenadine, two of which are Dutch reports. Four reports concerned male patients, three female and the sex was unspecified in one report. The age of the patients varied from 13 to 62 years (one patient with an unknown age). In two patients an atrioventricular block was reported concomitantly with the bradycardia, as adverse event. In one patient the blood potassium level was decreased to a not specified value.

The WHO database also contained three patients with atrioventricular block, specified as a first degree block in one patient, during the use of fexofenadine. It all concerned male patients with an average age of 32 years [range 26-37].

On the third of June 2009, the Eudravigilance database contained, besides one of the Dutch reports, nine reports of bradycardia associated with the use of fexofenadine (table 2). Striking is that three of these reports originated from doctors who experienced this suspected adverse drug reaction themselves. The proportional reporting ratio (PRR) for fexofenadine and bradycardia in the Eudravigilance database is 2.03 (95% CI 1.10-3.76).

No reports are present under MedDRA Preferred Terms "sinusbradycardia or sinoatrial block" in the Eudravigilance database. However, another four cases of atrioventricular block were reported (table 1).

Please note, patients H, J and M were reported in both the WHO and Eudravigilance database.

Table 1. Reports of fexofenadine and bradycardia in the Eudravigilance database

Patient, Sex, Age, Country of origin	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Clinical information
A F, 30.8. 1946 Japan	atorvastatin hyperlipidaemia fexofenadine allergic conjunctivitis		bradycardia QT-prolongation heaviness of head anti-allergic drug interaction	time to onset: four days for fexofenadine, two days for atorvastatin. recovery, first for QT-prolongation, later for bradycardia after withdrawal of both drugs
B F, 15 Germany	fexofenadine insect bite		bradycardia extrasystoles unspecified AV block	unspecified AV block, HR 45/min, bradycardia, dizziness, syncope, convulsions. ECG: AV block, extrasystoles, no QT-prolongation
C M, 65 India	fexofenadine acute rhinitis	digoxin amiodarone ramipril furosemide/ amiloride	bradycardia syncopal attack	withdrawal of fexofenadine, orcipraenaline treatment, recovery, multiple episodes of syncope after four days use of fexofenadine
D M, 80 Japan	fexofenadine urticaria		bradycardia dizziness nausea vomiting	positive dechallenge (and "intravenous drip") heart rate 45/minutes. (70-90 normal) on day of use of fexofenadine, doubt whether bradycardia caused dizziness and nausea or vice versa
E M, unspecified age, United States	fexofenadine pruritus NOS digoxin	levothyroxine insulin oxymetazoline potassium chloride	bradycardia (30/min) heart block	discontinuation of fexofenadine and all cardiac medication, normalisation to 60-70 bpm, attributed to interaction by reporting physician (patient involved)
F unspecified age (13 or 14) and unspecified sex United States	fexofenadine		bradycardia fainting	no information on action taken with drug and outcome of reaction
G F, 30.12. 1971 Brazil	fexofenadine allergic rhinitis		bradycardia mild dyspnoea right branch blocked	reporting physician is patient involved limited additional information

Patient, Sex, Age, Country of origin	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Clinical information
H F, 43 United States	fexofenadine multiple allergies		bradycardia (40 bpm) heart block first degree	withdrawal recovery
I F, 54 Italy	fexofenadine	phenobarbital orphenadrine clothiapine aspirin carbamazepine	bradycardia, hypotension, presyncope	very limited information, first degree AV block?, BAV1
J M, 26 United States	fexofenadine multiple allergies	levothyroxine	first degree AV block chest tightness	withdrawn, recovery, adverse reaction related to fexofenadine 540 mg overdose, clear ECG one month prior and one month after occurrence of reaction
K F, 72 Japan	fexofenadine allergic rhinitis	olopatadine quazepam magnesium oxide odium pciosulfate	third degree AV block	time to onset thirteen days, withdrawal, recovery, pacemaker insertion, apparent need for magnesium suppletion, breast cancer and hepatitis C in medical history
L Age and sexe unspecified United States	fexofenadine	clindamycin	third degree AV block	minimal clinical information provided
M M, 34 United States	fexofenadine sinusitis	omeprazole	bradytachyarrhythmia first degree AV block	two weeks, recovery after withdrawal, positive rechallenge
N F, 80 Japan	fexofenadine pollinosis	terbinafine pravastatin senna leaf	third degree AV block	latency twelve hours and ten minutes after ingestion of additional dose of fexofenadine, negative rechallenge

Mechanism

A couple of mechanisms might contribute to the possible cardiotoxicity of fexofenadine.

Fexofenadine is the pharmacologically active metabolite of terfenadine. In vitro studies have indicated that terfenadine may have arrhythmogenic effects similar to quinidine [7]. These studies have found that terfenadine is equipotent to quinidine as a blocker of the delayed rectifier potassium current in isolated feline myocytes. However, fexofenadine did not inhibit this current even at concentrations 30 times higher than the concentration of terfenadine producing a half-maximal effect [7].

It has been reported that fexofenadine can cause a prolonged QTc interval. The exact mechanism is unknown, but the drug might delay repolarization causing a prolonged QTc interval that may induce ventricular arrhythmias, including bradycardia, in susceptible individuals [8]. However, a prolongation of the QTc

interval is not reported in any of the Lareb cases and once in the Eudravigilance cases concerning bradycardia.

Another possible mechanism is the theory that fexofenadine is not completely selective for the H₁ receptor, but has also got some affinity for the H₂ receptor. H₂ receptor antagonists can cause bradycardia and even atrioventricular block [9,10].

Discussion and conclusion¹

Lareb received three recently the third serious reports of bradycardia associated with fexofenadine. All patients were admitted to hospital for adequate treatment, in one patient resuscitation was needed. The association is supported by disproportionality in the Lareb database and Eudravigilance database, but neither by the database of the WHO nor by publications in the literature. However, single reports in the Eudravigilance and WHO database are suggestive for a causal relationship. It is not sure yet which mechanism is responsible for this serious, possible adverse drug reaction of fexofenadine. In seven Eudravigilance cases an AV block was reported, in three of them concomitantly with bradycardia, which might indicate influence of fexofenadine on the AV node. Given the possible consequences of bradycardia and the fact that this product is available as an OTC drug, a clear warning in the SmPC should be stated.

- Signal of bradycardia associated with the use of fexofenadine.
- Bradycardia should be mentioned in the SmPC of fexofenadine.

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¹ This signal is currently (January 2010) analysed in more detail.

1.2. SSRIs and aggression

Introduction

The serotonin reuptake inhibitors (SSRIs) are prescribed for the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder, panic disorder, generalized anxiety disorder, and posttraumatic stress disorder.

SSRIs on the Dutch market are citalopram (Cipramil®), escitalopram (Lexapro®), paroxetine (Seroxat®), fluoxetine (Prozac®), sertraline (Zoloft®) and fluvoxamine (Fevarin®). Venlafaxine (Efexor®) in a dosage less than 150 mg is also considered an SSRI.

Recently, there has been much interest in the possible relation between aggression and the use of SSRIs. This is due to recent murder cases in the Netherlands, where a connection was made with SSRI usage [1].

The Dutch SmPCs of the SSRIs describe agitation and manic reaction as possible adverse drug reactions, but aggression and murder ideation are not described [2-7].

Reports

On June first 2009, the Lareb database of the Netherlands Pharmacovigilance Centre Lareb contained 24 reports of aggression or related ADRs associated with the use of SSRIs. The time to onset was one week or less in eight cases, 2-6 weeks in six cases, 1.5 year in one case and unknown in nine cases. It concerned the following SSRIs:

Paroxetine	8 cases
Citalopram	5 cases
Fluoxetine	4 cases
Fluvoxamine	4 cases
Escitalopram	2 cases
Sertraline	1 case

Table 1. Reports of aggression associated with the use of SSRIs.

Patient, sex, age, source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Original description by the reporter	Time to onset, outcome
A 10028 F, 29 General Practitioner	fluoxetine capsule 20mg		aggressive reaction	aggressive thoughts	6 days discontinued not reported
B 25667 M, 32 Pharmaceutical Company	fluvoxamine tablet 100mg		agitation, aggressive reaction, nausea	impulsive aggression	4 days discontinued not reported
C 27271 M, 76 Pharmaceutical Company	fluvoxamine tablet 50mg		hyperkinesia, amnesia, aggressive reaction, depersonalization, disorientation, hallucination visual	aggression	not reported unknown not reported

Patient, sex, age, source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Original description by the reporter	Time to onset, outcome
D 32622 F, 65 Pharmacist	paroxetine tablet 20mg Depressive episode	clonazepam tablet 0.5mg	hyperactivity, paranoid reaction, aggressive reaction	aggressiveness	3.1 weeks dose reduction recovered
E 34478 F, 18 Pharmacist	fluoxetine capsule 20mg	OAC tablet: ethinylestradiol /desogestrel	balance difficulty, aggressiveness	aggression	1 week discontinued unknown
F 36483 M, 10 Pharmaceutical Company	fluvoxamine tablet 50mg Depressive episode		suicidal tendency, aggressive reaction, irritability	physically aggressive	not reported discontinued unknown
G 37338 = 44991 = 37369 M, 33 Pharmaceutical Company	sertraline tablet 50mg		delusion, sensory hallucinations, psychotic reaction nos, aggressiveness	violent behavior, almost killing of girlfriend and 2-year-old son	3 days discontinued recovered
H 37487 M, 22 Pharmacist	fluoxetine tablet 20mg Burn		restlessness marked, thoughts of self harm, aggressive reaction	aggressive	day discontinued recovered
I 37696 M, 35 General Practitioner	paroxetine tablet 20mg Depressive episode		aggression aggravated	aggravation of aggressive symptoms	1,5 year discontinued recovered
J 37721 M, 11 Pharmacist	paroxetine tablet 20mg, ritalin tablet 10mg		sleep disorder, aggressiveness, self mutilation, character change	aggressive behavior	not reported discontinued recovered
K 37863 M, 23 Specialist doctor	fluvoxamine tablet 100mg Depression	lorazepam tablet 1mg risperidon tablet 1mg, biperidene tablet 2mg	aggressiveness	growing irritation, anger, aggression, resulting in homicide of his aunt and grandmother	6 weeks discontinued recovered
L 39137 M, 48 Specialist doctor	paroxetine tablet 40mg		aggressive reaction	severe impulse control disorder, resulting in fights. Attacked his boss; had to be stopped by 3 colleagues	several weeks no change unknown
M 39645 M, 34 General Practitioner	fluoxetine disp tablet 20mg Depressive episode		aggressiveness	verbal aggression, violence	not reported no change recovered
N 39646 M, 45 General Practitioner	citalopram tablet 40mg Depressive episode	diazepamum tablet 2mg	aggressiveness	verbal aggression	not reported unknown recovered

Patient, sex, age, source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Original description by the reporter	Time to onset, outcome
O 53709 M, 48 Consumer	paroxetine tablet 20mg Depression	bromazepam m tablet 3mg, venlafaxine tablet 75mg	suicidal tendency, aggressive reaction	aggressiveness	not reported discontinued not recovered
P 53981 F, 37 Consumer	citalopram tablet 20mg		aggressiveness, libido decreased	aggressive	not reported not reported unknown
Q 54840 M, 23 Consumer	citalopram drops 40mg/ml Anxiety	risperidon tablet 2mg	malaise, paranoia, aggressiveness	aggressive	1 day discontinued not recovered
R 57125 F, 28 Consumer	paroxetine tablet 20mg Depression		suicidal ideation, restlessness, aggressiveness, impulsive behaviour, self mutilation	aggression towards environment and herself, was placed in isolation cell	4 weeks dose reduction recovered
S 57704 M, 53 Consumer	paroxetine tablet 20mg		therapeutic response unexpected with drug substitution, aggressiveness	severe aggression	not reported no change recovered
T 60252 F, 39 Consumer	escitalopram tablet 10mg Depression	Salmeterol /fluticason 50/250mcg 60do	aggressiveness	aggressive behavior	4 weeks discontinued recovered
U 61293 M, 19 Consumer	citalopram tablet 40mg Psychiatric disorder NOS	risperidon tablet 4mg	suicidal ideation, aggressiveness	aggression	3 weeks no change not recovered
V 61981 F, 28 Consumer	escitalopram tablet 10mg Depression		myalgia, aggressiveness, galactorrhoea	aggression	4 weeks discontinued recovered
W 70367 M, 36 Pharmacist	paroxetine tablet 30mg Depression		food interaction, aggressiveness, impulse-control disorder	murder ideation towards son: temporary separation from kids	1 day unknown unknown
X 77918 M, 20 Hospital Pharmacist	citalopram tablet 40mg Depression		aggressive behavior	aggressive behavior: life- threatening for hospital staff	7 days no change unknown

Other sources of information

Literature

Although several studies describe a role for serotonin in aggression [8,9], there is no consensus in literature about the effect that the use of SSRIs may have on aggression. Some studies describe a direct link between use of SSRIs and increased violence and aggression [10-12] while other studies do not find any support for this association [13,14].

In a number of trials SSRIs have been investigated for the treatment of aggression. In a review on the pharmacotherapy of aggressive behaviour, of ten available placebo controlled RCTs with antidepressants six (four of which SSRIs) showed positive outcome for the antidepressant in clinically different groups of patients [15]. The conclusion is that there is weak evidence for the use of antidepressants in the management of aggression across a diversity of diagnoses.

Other databases

On June first 2009, the Lareb database of the Netherlands Pharmacovigilance Centre Lareb contained 24 reports of aggression or related ADRs associated with the use of SSRIs. This supports a causal relationship between SSRIs and aggression (ROR = 1.98; 95% CI 1.32 - 2.96).

On June 30, 2009, the WHO database of the Uppsala monitoring centre contained 4,158 reports of aggressive reaction in association with SSRIs. This supports a causal relationship (ROR = 6.6; 95% CI 6.6 – 7.0).

On July 1st the Eudravigilance database contained 700 reports of aggression in SSRI using subjects. The reported reaction was reported serious in all but two cases. Sex was not specified in 16 cases, 387 male and 297 female patients were involved. Aggression formed part of a reaction leading to decrease in 40 cases and led to disability in 36 cases. Patients' ages ranged from 3 to 90 years. Fifty-one patients were 12 years or younger of age.

Prescription data

The number of patients using SSRIs in the Netherlands is shown in Table 2.

Table 2. Number of users of SSRIs in the Netherlands between 2004 and 2008. (Source: Drug Information System of the Dutch Health Care Insurance Board (GIP))

	2004	2005	2006	2007	2008
N06AB serotonin reuptake inhibitors	568,820	548,490	547,090	523,790	556,060

Mechanism

SSRIs increase serotonergic activity in the central nervous system by inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT).

Serotonin is supposed to have a role in the inhibition of impulses, the regulation of emotions and social functioning, which are domains linked to aggression [9].

Soon after starting treatment with SSRIs, akathisia, temporary increase in anxiety and/or paradoxical worsening of the individual's depressive agitation can occur; this may trigger for reactive aggressive behavior.

However, underlying disease and environmental influences make it difficult to demonstrate an indisputable relation between aggression and the use of SSRIs.

Conclusion

The Lareb reports suggest a possible relation between SSRIs and aggression. WHO data support this association. Special attention is asked for this association, considering the nature of the adverse drug reaction and the possible consequences.

- Further attention for aggression related to the use of SSRIs is warranted.

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1.3. Topical imidazole derivatives and drug interactions

Introduction

The imidazole derivatives are potent antifungal agents. In the Netherlands the imidazole derivatives bifonazole, clotrimazole, econazole, ketoconazole, miconazole and sulconazole are registered for topical administration as creams, ointments, gels or sprays. They have all been registered between 1971 and 1986 [1-7]. When used topically, these drugs are indicated for *the treatment of mycotic infections of the skin, such as cutaneous candidosis, pityriasis versicolor and seborrheic dermatitis caused by dermatophytes, candida and pitysporum species and yeasts* [1,2,4,7]. Currently, ketoconazole and bifonazole are prescription only drugs and econazole, miconazole, clotrimazole and sulconazole are available over the counter.

Imidazole derivatives inhibit the synthesis of ergosterol by competitive inhibition of the cytochrome (CYP) P450 enzyme lanosterol-14 α -demethylase [8]. This enzyme is responsible for the transformation of lanosterol into ergosterol. The decreased ergosterol concentration causes an impairment of the fungal cellular membrane which leads to an altered cellular membrane permeability and the loss of essential cell contents. Besides, the imidazoles have some activity against gram-positive bacteria [1-7].

It is known that systemic administration of ketoconazole leads to inhibition of the hepatic enzyme CYP3A4 and systemic and vaginal administration of miconazole leads to inhibition of CYP3A4, CYP2C9 and CYP2C19 [8-13]. These inhibitions could lead to a decrease in the clearance of drugs which are metabolized through these systems, such as ciclosporin, phenytoin, coumarin anticoagulants and some statins. The systemic absorption of topical imidazole derivatives is thought to be low. All SmPCs of topical imidazoles, except for sulconazole, mention a systemic absorption of 2% or less [1-7]. The SmPCs of miconazole cream and miconazole/hydrocortisone cream and ointment state that considering the low systemic absorption after topical administration, clinical relevant interactions occur very rarely [4-5]. In the SmPCs of other topical imidazoles no possible interactions are mentioned [1-3,6,7]. This report describes the possible relation between the topical use of imidazole derivatives and the occurrence of drug interactions.

Reports

On April 8, 2009, the database of the Netherlands Pharmacovigilance Centrum Lareb contained 17 reports of possible drug interactions associated with the topical use of an imidazole derivative. 11 reports concerned an interaction between a topical imidazole and a coumarine derivative (table 1) which led to an increase in the international normalized ratio (INR), five reports concerned an interaction with a statin and one report showed an interaction with an anti-epileptic drug (table 2). Three reports originated from a general practitioner, one from the Federation of Dutch Thrombosis Services, five from a pharmacist, two from a nursing home practitioner, two from a consumer and four from a specialist doctor.

All patients used the coumarine, statin or anti-epileptic drug for months to years before the imidazole derivative was started. The times to onset in both tables concern the time from the start of the imidazole derivative to the beginning of the adverse drug reaction(s). The imidazole derivative was withdrawn in 13 patients, eight patients recovered and three patients were recovering at time of reporting. In one patient a positive rechallenge was reported. Ten reports concerned the use of miconazole cream, five reports ketoconazole cream, one econazole spray and one bifonazole cream.

Table 1. Reports of possible interaction of topical imidazole derivatives and a coumarine

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome Relevant clinical info
A 70886 F, 77 Specialist doctor	miconazole cream 20mg/g dermatomycosis on and under breasts phenprocoumon	furosemide spironolactone simvastatin acetylcysteine losartan carvedilol	drug interaction potentiation, INR increased to 20	12 days unknown recovered
B 43273 F, 80 Fed. Dutch Thromb. Services	miconazole cream 20mg/g application around anus phenprocoumon		coagulation time increased, INR increased to 10.8	2 weeks discontinued recovered
C 53264 M, 57 Pharmacist	ketoconazole cream 20mg/g rash from tick bite acenocoumarol	doxycycline miconazole/ hydrocortisone cream (as needed)	drug interaction, INR increased	1 week discontinued recovered heterozygote for 2C19*2
D 60845 M, 68 Pharmacist	bifonazole cream 10mg/g onychomycosis (under occlusion), phenprocoumon	simvastatin	INR increased to 5.3	1 week discontinued recovering
E 44960 F, 77 Pharmacist	miconazole cream 20mg/g rash under and on the breast phenprocoumon	furosemide simvastatin carvedilol glimepiride metformin losartan	INR increased to 20	12 days no change unknown
F 22601 M, 74 General Practitioner	econazole dermal spray 10 mg/g fungal infection back acenocoumarol		prothrombin time prolonged, INR increased to 15.8	not reported unknown not reported
G 59743 F, 69 Nursing home practitioner	miconazole cream 20mg/g mycosis fungoides (large surface) acenocoumarol	chlortalidone fosinopril metoprolol bisacodyl glimepiride metformin	INR increased to 12.1	1 week no change unknown
H 70885 M, 73 Specialist doctor	miconazole cream 20mg/g doxycycline tablet 100mg respiratory tract infection phenprocoumon	vitamin B complex insulin flammazine levodopa/carbidopa lactulose paracetamol omeprazole motilin	drug interaction potentiation, INR increased to 7.4	1 day discontinued unknown

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome Relevant clinical info
I 81519 F, 98 Nursing home practitioner	miconazole cream 20mg/g miconazole/hydrocortisone ointment dermatitis fungal under breasts acenocoumarol	esomeprazole movicolon paracetamol oxazepam prednisolone sodium phosphate, spironolactone estriole epoetine alpha alfacalcidol ferro sulphate cipramil bumetanide acebutolol nitroglycerin	drug interaction potentiation, INR increased to > 8	12 days discontinued unknown
J 70136 M, 59 Consumer	miconazole cream 20mg/g dermatomycosis groins and armpits acenocoumarol	valproic acid sotalol losartan flecainide	drug interaction potentiation, INR increased to 5.9	2 weeks dose discontinued not recovered
K 82897 F, 88 General Practitioner	vascular occlusion, miconazole cream 20mg/g erythema acenocoumarol	simvastatin nitrendipine alendronic acid tolbutamide irbesartan/ hydrochlorothiazide	drug interaction potentiation, epistaxis, INR increased to 5.5	1 month discontinued unknown

All patients in table 1 were using a coumarine when the topical imidazole derivative was introduced. The time between the start of the imidazole and the increase of the INR was 1-2 weeks. In one patient a latency of one month was reported. The difference in latency might be explained by differences in the interval of regular INR controls. The INR of patients A, B and C normalized after discontinuation of the topical imidazole derivative. Patients D and J were recovering at the time of reporting after withdrawal of the imidazole derivative. The absorption of the topical used imidazoles could have been influenced by the application site of the drug. In patient F the cream was applied on a large surface, patient B used the cream around the anus which could have led to absorption through the mucous membranes and in patients A, D, E, I and J the cream was (partly) used under occlusion (for example application under the breasts in women). The maximum INR after application of the imidazole creams varied from 5.3 to 20.

Table 2. Reports of possible interaction of topical imidazole derivatives and statins and anti-epileptic drugs

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
L 83697 F, 49 Specialist doctor	ketoconazole cream 20mg/g atorvastatin 20mg hypercholesterolemia	acetylsalicylic acid losartan	drug interaction, rhabdomyolysis (CK>8000)	unknown discontinued atorvastatin recovering
M 55882 M, 53 Pharmacist	miconazole cream 20mg/g dermatitis fungal large surface trunk simvastatin 20mg hypercholesterolaemia	mesalazine	drug interaction, myalgia	2 days discontinued miconazole recovered + rechallenge reported

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
N 29492 M, 46 General Practitioner	ketoconazole cream 20mg/g seborrhoeic dermatitis atorvastatin 20mg pure hypercholesterolaemia	colestipol aspirine	tiredness, muscle weakness	1 day discontinued ketoconazole recovered
O 62101 F, 70 Pharmacist	ketoconazole cream 20mg/g eczema armpits, simvastatin 20mg	acetylsalicylic acid metoprolol	drug interaction, myalgia	2 weeks discontinued ketoconazole recovered
P 65620 M, 66 Consumer	ketoconazole cream 20mg/g dermatomycosis armpits, simvastatin 40mg		drug interaction, myalgia	week discontinued ketoconazole not recovered
Q 85713 M, 7 Specialist doctor	miconazole cream 20mg/g mycoses behind both ears clobazam tablet 10mg epilepsy	levetiracetam movicolon carbamazepine	drug interaction intoxication	months discontinued recovered

The patients in table 2 were all using a statin when a topical imidazole derivative was started. The time to onset of the adverse drug reaction of the statin was reported in four of the five patients and varied from one day to two weeks. In patient M a positive rechallenge was reported. The absorption of the imidazole derivative could have been influenced by application on a large surface in patient M and under occlusion by using the cream in the armpits in patients O and P. Patients M, N and O recovered after withdrawal of the imidazole derivative, one patient (P) did not recover after withdrawal of the ketoconazole and patient L was recovering at the time of reporting after discontinuation of atorvastatin. Patient Q presented with symptoms of fatigue a couple of months after the start of miconazole cream. Clobazam had been used for more than two years. A blood test showed a major increase in plasma level of the clobazam metabolite desmethylclobazam with a normal clobazam plasma level. Normally the proportion clobazam:desmethylclobazam is one to eight [14]. In this patient the proportion was one to fifty. The patient recovered after discontinuation of both miconazole and clobazam.

Other sources of information

SmPC

The SmPCs of miconazole cream and miconazole/hydrocortisone ointment and cream state that considering the low systemic absorption after topical administration, clinical relevant interactions occur very rarely [4-5]. In the SmPCs of other topical imidazoles no possible interactions are mentioned [1-3,6,7]. The SmPCs are not consistent about the bioavailability of the topical creams. The SmPC of ketoconazole cream states that after topical application no detectable plasma levels were found, which means a concentration of lower than five microgram per liter. In babies from one to five months with seborrheic dermatitis plasma levels up to 133 microgram per liter were measured [1]. The SmPC of clotrimazole cream mentions a systemic absorption of less than 2% of the applied dose [6]. The SmPCs of both miconazole and econazole cream state that the bioavailability after topical application is less than 1% [4,7]. The SmPC of

miconazole adds that systemic absorption has been detected after repeated topical administration in children with nappy rash [4]. The product information of sulconazole cream mentions a bioavailability of 10% after application of the cream on normal skin [3]. The SmPC of bifonazole does not give any information about bioavailability [2].

Literature

Only one article was published about the biological availability of topical administration of the in the Netherlands registered imidazole derivatives. In 1996 an analytical method using high-performance liquid chromatography for the determination of miconazole in human plasma was published [15]. Pershing *et al.* investigated the *in vivo* pharmacokinetics and pharmacodynamics of topical ketoconazole and miconazole in six people. They detected a systemic concentration for both drugs. Unfortunately the exact percentage or concentration was not mentioned [16].

Despite this limited information about the absorption and bioavailability of topical imidazoles, a couple of case reports have been published about the use of topical imidazole derivatives and drug interactions. In 1992, the effect of topical ketoconazole on the metabolism of oral ciclosporin was investigated in five patients with allergic contact dermatitis. They were given a six-day course of ciclosporin 1 mg/kg/day and applied ketoconazole 2% cream to an area of one arm and an inert base on the other. No significant difference in response was found between the two sites which indicates that topical ketoconazole does not potentiate oral ciclosporin [17]. The British Medical Journal published in 2002 a case report about the loss of control of anticoagulation in a patient taking over the counter miconazole cream for flexural intertrigo. The patient had been stable for months on warfarin with an INR ranging between 2.2 and 3.1. After two weeks of applying topical miconazole in his right groin his INR increased to 21.4 [18]. Lang *et al.* reported in 2006 a 79-year-old man, taking long-term warfarin, who was given econazole cream for a fungal groin infection. Within one week of starting to apply the cream, he noticed bruising. His INR was increased from 2.2 to 12 [19]. Another case report concerns an 84-year-old woman who had been receiving acenocoumarol 4 mg per day for ten years for episodes of atrial fibrillation and recurrent deep venous thrombosis. Seventeen days after she started using econazole lotion 1% for a dermatitis affecting 12% of the body surface she suffered from overanticoagulation and a life-threatening laryngeal hematoma [20]. Alexandra *et al.* described in 2008 six cases of overanticoagulation with coumarin therapy in patients treated with a topical azole. Four of the patients had an INR greater than 9.0. Three of the patients were heterozygous for a CYP2C9 variant allele, all with INR values greater than 11.0 (highest INR>20). Three patients applied econazole (lotion, cream or powder) to the vulva under a disposable diaper. The other three patients applied econazole cream to their buttocks, groin and trunk. The authors conclude that cutaneous application of azole to large and/or relatively penetrable areas increases the risk for systemic absorption, thereby leading to marked systemic effects, especially when applied under occlusive diapers [21]. No case reports with a possible interaction between a topical imidazole derivative and a statin or an anti-epileptic drug were found.

Databases

In April 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained 17 reports of a possible interaction between topical imidazole derivatives and other drugs. Due to varieties in encoding the interactions and/or adverse drug reactions in the system and the different drugs concerned, it is not possible to determine a reporting odds ratio for this association.

Unfortunately it is also not possible to extract information about possible interactions related to the use of topical imidazole derivatives from the database of the World Health Organization (WHO) and the Eudravigilance database.

Mechanism

Imidazole derivatives can interfere with the metabolism of other drugs by influencing the cytochrome P450 system. Some imidazole derivatives can inhibit certain enzymes from the cytochrome P450 system. Inhibition of these enzymes leads to an increased plasma level of drugs metabolized by these enzymes.

Concomitant use of an imidazole derivative and a drug which metabolism could be influenced by this antifungal agent, could lead to an increased plasma level of the drug concerned, more adverse drug reactions and even intoxication.

Ketoconazole is a potent inhibitor of CYP3A4. Miconazole is a potent inhibitor of CYP2C9 and a less potent inhibitor of CYP3A4 [22]. In the literature it has been prescribed that miconazole is also a potent inhibitor of CYP2C19 [13]. Econazole is structurally similar to miconazole and inhibits CYP2C9 and CYP3A4 [22]. No information is available about the possible influence of bifonazole and sulconazole on the cytochrome P450 system, although influence is expected due to chemical structure similarities of the imidazole derivatives.

Warfarin, phenprocoumon and acenocoumarol are racemic mixtures of S- and R-enantiomers. These enantiomers are metabolized by different cytochrome P450 isoenzymes. The S-enantiomers of all three coumarines are mainly metabolized by CYP2C9. The R-enantiomers are metabolized by different other cytochrome P450 isoenzymes such as CYP2C19, CYP3A4 and CYP1A2. Inhibition of these enzymes can lead to an increased plasma concentration and systemic effect of coumarines (increased international normalized ratio) [22]. The Federation of Dutch Thrombosis Services mentions in their protocol that the effect of application of topical miconazole on a large surface or under occlusion on this possible interaction is not yet known [23].

Simvastatin and atorvastatin are metabolized by CYP3A4. Atorvastatin is less sensitive to CYP3A4 inhibition than simvastatin, because AUC and C_{max} increase to a lesser extent with strong CYP3A4 inhibitors [24]. Combined use of systemic ketoconazole, miconazole or econazole and simvastatin or atorvastatin could therefore lead to increased plasma levels of these cholesterol synthesis inhibitors and to an increased risk for (serious) adverse drug reactions [25].

Clobazam is metabolized by CYP3A4 and in a lesser extent CYP2C19 to the active metabolite desmethylclobazam. Desmethylclobazam is metabolized by mainly CYP2C19 to a pharmacologically inactive product [26]. Miconazole can influence the metabolism of clobazam by inhibition of CYP3A4 and CYP2C19. Concomitant use could lead to accumulation of clobazam and desmethylclobazam. In the case reported to Lareb (patient Q) miconazole also caused inhibition of the metabolism of carbamazepine by CYP3A4 as carbamazepine is metabolized by this enzyme. Carbamazepine also induces CYP3A4 which could have led to an increased conversion of clobazam in desmethylclobazam. This could explain the extreme increase in the plasma level of desmethylclobazam with a normal clobazam level in this patient.

Discussion

Topical imidazole derivatives are used quite regularly. The number of patients prescribed a topical imidazole derivative in 2007 can be seen in table 3. The actual number of users is higher as econazole, miconazole, clotrimazole and sulconazole are also available over the counter.

Table 3. Number of patients that were prescribed a topical imidazole derivative in 2007 [27].

Drug	Number of patients
Clotrimazole	15
Miconazole	4,831
Econazole	0
Ketoconazole	287,350
Sulconazole	34,237
Bifonazole	1,186
Miconazole / Hydrocortisone	999

The interaction between systemically used imidazole derivatives and drugs metabolized by the cytochrome P450 system is well known. However, the possible effect of topical administered imidazole derivatives on these enzymes has only been published a couple of times and is not recognized in protocols of doctors and pharmacists. The Federation of Dutch Thrombosis Services is currently implementing the possibility of interactions of topically used imidazole derivatives and coumarines in their protocol.

On top of that little is known about the systemic absorption of topical administered imidazole derivatives. In most of the 17 reports received by the Netherlands Pharmacovigilance Centre Lareb, the application site could be an explanation for systemic absorption as application under occlusion, on large surfaces and close to mucous membranes were reported. The influence of application site on the risk of these interactions was confirmed in the literature [21]. As the systemic absorption in clinical trials for topical imidazoles was either below detectable levels or under 2%, except for sulconazole with an absorption of 10%, the influence of application site and surface must be taken into account when determining the risk of an interaction between an imidazole derivative and a drug metabolized by CYP3A4, CYP2C9 and/or CYP2C19 in an individual patient. Besides, genetic differences could influence the risk of developing a clinically relevant drug interaction when using a topical imidazole derivative. Genetic variabilities have been described for CYP2C9 [22]. Poor metabolizers have a lower activity of certain enzymes of the cytochrome P450 system. Therefore poor metabolizers have a higher risk for drug interactions with a low systemic concentration of an imidazole derivative than normal metabolizers do.

Conclusion

Lareb received 17 reports of drug interactions associated with the use of a topical imidazole derivative. These reports concerned the topical imidazoles miconazole (n=10), ketoconazole (n=5), econazole (n=1) and bifonazole (n=1). Systemic absorption and therefore the risk for interactions on the cytochrome P450 system could have been influenced by application under occlusion, on a large surface and close to mucous membranes. Genetic differences could influence the susceptibility for this interaction.

- Topical administration of imidazole derivatives could initiate cytochrome P450 drug interactions, especially when used under occlusion, on a large surface or on/close to mucous membranes.
- The possibility of systemic absorption and drug interactions should be mentioned in the SmPC of the topical imidazole derivatives miconazole, ketoconazole and econazole.

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1.4. Omeprazole and coumarine interactions

Introduction

Omeprazole (Losec®) is a proton pump inhibitor (PPI) which has been registered in the Netherlands since November 1988. It is indicated for use in *gastroduodenal ulcerative disease, acid relate dyspepsia, reflux-oesophagitis or reflux symptoms and in Zollinger-Ellison's syndrome* [1]. Furthermore omeprazole is used as prophylactic treatment in people at risk for drug related erosive or ulcerative gastric disorders. With 1,025,000 users in 2007 omeprazole is the most frequently used PPI [1]. Among its most common adverse reaction are headache and gastro-intestinal symptoms [2].

In the Netherlands both acenocoumarol and phenprocoumon (Marcoumar®) are coumarine derivates 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. VKAs have a narrow therapeutic range. 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. Internationally, warfarin is more commonly used. Differences in these three preparations are predominantly limited to pharmacokinetic properties. As warfarin, acenocoumarol and phenprocoumon are racemates.

No information on effects of omeprazole on coumarine treatment is mentioned in the product information texts of the brand preparations involved [1,3,4]. In SmPCs of some generic preparations the possibility of coumarine interactions is addressed, however only addressing the possibility of interaction with warfarin, a drug very rarely used in the Netherlands. Coumarin interactions are addressed in the Dutch SmPC for esomeprazole [5].

This report describes possible coumarine potentiating effects associated with omeprazole use.

Reports

Until April 1st 2009 the Netherlands' Pharmacovigilance Centre Lareb received nine reports of potentiation of coumarine-induced coagulation effects associated with use of omeprazole (table 1). Eight cases were reported by physicians from thrombosis services. In four reports INR increase was such that bleeding risks may have posed a real threat with reported INRs above six. Increases in INR occurred predominantly within days after onset of PPI therapy, with a maximum of eleven days. No cases that led to lowering of INR and upward adjustment of coumarin treatment after start of omeprazole treatment were reported. Lareb received seven cases of potentiation of VKA anticoagulatory effect after start of esomeprazole. Cases of coumarin potentiation by other PPIs have not been reported.

Table 1. Reports of possible interaction of omeprazole and a coumarine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction Maximum INR	Time to onset, Action with drug outcome
A 78206 F, 73 Fed. Dutch Thromb. Services	acenocoumarol atrial fibrillation, omeprazole capsule 20mg shoulder pain	ibuprofen 400mg	drug interaction potentiation, INR increased INR >9.0	1 week discontinued recovered
B 70891 M, 56 Fed. Dutch Thromb. Services	acenocoumarol coronary artery disorder, omeprazole tablet 10mg	pravastatin 10mg gemfibrozil 600mg bisoprolol 5mg	drug interaction potentiation, INR increased INR 8.5	1 week discontinued recovered
C 82911 M, 72 general practitioner	acenocoumarol paroxysmal atrial fibrillation, omeprazole capsule 40mg gastroesophageal reflux	valsartan 80mg digoxin 0,25mg flecaïnide 200mg psyllium	drug interaction potentiation, blistering of mouth, haematoma, INR increased INR 7.3	5 days discontinued recovered
D 78208 F, 63 Fed. Dutch Thromb. Services	acenocoumarol atrial fibrillation, omeprazole capsule 20mg	metformin non specified insulin diclofenac 50mg	drug interaction potentiation, INR increased INR 7.1	5 day no change unknown
E 73971 F, 79 Fed. Dutch Thromb. Services	phenprocoumon vascular disorder, omeprazole tablet 10mg	nebivolol 5mg, isosorbide mononitrate 10mg digoxin 0,125mg triamterene 50mg captopril 12,5mg bumetanide 1mg	drug interaction potentiation, INR increased INR 5.2	1 day unknown not yet recovered
F 73970 M, 57 Fed. Dutch Thromb. Services	acenocoumarol atrial fibrillation, furasone 50mcg omeprazole tablet 10mg	perindopril 2mg amlodipine 5mg	drug interaction potentiation, INR increased INR 5.1	1 day unknown unknown
G 78207 F, 54 Fed. Dutch Thromb. Services	phenprocoumon atherosclerosis of arteries of the extremities, omeprazole capsule 20mg	-	drug interaction potentiation, INR increased INR 5.0	11 days no change recovered

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction Maximum INR	Time to onset, Action with drug outcome
H 73972 M, 82 Fed. Dutch Thromb. Services	acenocoumarol deep venous thrombosis femoral, omeprazole tablet 10mg	-	drug interaction potentiation, INR increased INR 5.0	1 day unknown recovered
I 73973 M, 60 Fed. Dutch Thromb. Services	acenocoumarol coronary artery bypass, omeprazole tablet 10mg not specified glimepiride not specified	metoprolol retard 47,5mg metformin 500m spironolactol 25mg ramipril 2,5mg furosemide 40mg retardor 10mg, mono cedocard 25mg	drug interaction potentiation, INR increased INR 4.8	1 day no change unknown

Other Sources

Literature

Information on omeprazole interactions with acenocoumarol or phenprocoumon is limited. Enderle, Mueller and Grass present two cases of potentiation of phenprocoumon induced by omeprazole [6], whereas Garcia *et al* present one case of acenocoumarol potentiation by omeprazole use [7]. Given its wider use internationally, more information on warfarin reactions is present. In several review articles [8-10], guidelines [11] and in the FDA drug information [12] it is warned to use omeprazole with caution in people using warfarin.

In two studies, the effect of omeprazole on anticoagulatory effects have been studied. The first, a retrospective observational database study, compared INRs in 118 acenocoumarol using patients, five to seven days, after start of omeprazole. Omeprazole users were compared with subjects that did not use concomitant therapy [13]. The second study concerns a small placebo-controlled trial (n=8) of three days duration [14]. Both studies concluded that omeprazole has no effect on coumarine anticoagulatory therapy.

Databases

The nine cases of INR increase for omeprazole result in disproportionality in the database of the Netherlands Pharmacovigilance Centre Lareb, Reporting Odds Ratio (ROR) 8.2, 95% confidence interval 4.1 - 16.3).

Eudravigilance database

On April 15 the Eudravigilance database contained 32 reports of increases in INR in omeprazole users. The reaction was rated serious in 31 cases. Sixteen male patients were involved and fifteen female patients. Sex was not specified in one case. Age ranged from 29 to 91 years.

Reportedly six reactions led to decease, seven to life threatening symptoms. Hospitalisation was required in fifteen cases, in no reports disability was reported.

WHO:

The WHO Collaborating Centre database contained eighteen reports of omeprazole-associated INR increases.

Mechanism

Omeprazole has CYP 2C19 inhibitory effects, progressing in the first week of use and more limited effects on other CYP systems (CYP 2C9 and CYP3A4). By the effect on CYP2C19, it may slow the metabolism of the R-enantiomer of acenocoumarol, which is the active component of this drug due to its longer half time, compared to the very short half time of the S-enantiomer. Especially in poor CYP 2C19 metabolisers, using acenocoumarol this may lead to increases of acenocoumarol plasma values and increases in INR.

This mechanism does not explain INR increases in phenprocoumon and warfarin users. In these two drugs, half-times differ less between both enantiomers than in acenocoumarol. Subsequently, in phenprocoumon and warfarin, the more potent S-enantiomere acts as most effective component. The S-enantiomeres of coumarines are metabolised by CYP2C9, which is inhibited to a lesser degree than CYP2C19 by omeprazole. One of the mechanisms postulated is competition between omeprazole and phenprocoumon for CYP 2C9 binding sites in CYP2C19 deficient individuals [6].

Effects of omeprazole on action of coumarins through other systems, like VKORC1, cannot be excluded. However these are not supported by findings published in literature [15].

Discussion

The potentiating effect of omeprazole on acenocoumarol and phenprocoumon is demonstrated in nine generally well documented cases. Furthermore this association is supported by known effects of esomeprazole on VKA anticoagulation. Since maintaining a strict control of vitamin K-inhibition is vital, both reports of potentiation and inhibition of coumarines are clinically highly relevant. Through coumarine monitoring programs, patients' coumarine use is strictly regulated and reports of INR lowering might be expected to be reported. The absence of these reports may be considered as a support for the association described in this report. In all reports the PPI was added to the coumarin, which excludes instability of anticoagulation in the initial phase of coumarin treatment. In literature, two studies are presented in which evidence for coumarine potentiating effects of omeprazole is lacking [13,14].

Compared to the use of VKAs and omeprazole, the number of reports is relatively small, fitting in polymorphism affecting only a minor part of the general population. In two studies, it was concluded that omeprazole has no effects on coumarine action. However these studies either had a short duration, or were limited in size. This may hamper detection of averse effects of omeprazole in subgroups of patients with impaired metabolism due to CYP polymorphisms.

Conclusion

Lareb received nine reports of increases in INR after start of omeprazole, possibly related to CY2C19 interaction. In almost half of the cases involved serious increases of coagulability (INR greater than six). The possibility of this interaction should be mentioned in sections 4.4., 4.5 and 4.8 of the product information of omeprazole, esomeprazole, acenocoumarol and phenprocoumon.

- The possibility of potentiating effects of omeprazole on coumarines should be addressed in the SmPCs of these products

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1.5. Adalimumab and pustular psoriasis

Introduction

Adalimumab (Humira®) is a fully human recombinant monoclonal immunoglobulin G1 antibody expressed in Chinese hamster ovary cells that inhibits the action of tumor necrosis factor- α (TNF- α) by binding specifically to TNF- α and neutralizing the biological function of TNF- α by blocking its interaction with the p55 and p75 cell surface TNF receptors [1]. Adalimumab was granted marketing authorization on 8 September 2003 in Europe [1].

Therapeutic indications include rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis. In RA adalimumab is used either as monotherapy or in combination with methotrexate in patients with an inadequate response to classic disease-modifying antirheumatic drugs. Adalimumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to, or have a contraindication for other systemic therapy including cyclosporine, methotrexate or PUVA [1].

The SmPC of adalimumab mentions psoriasis as an uncommon adverse drug reaction, but pustular psoriasis is not mentioned [1].

This report describes pustular psoriasis in association with the use of adalimumab.

Reports

Excluding one duplicate report by the marketing authorization holder, the Netherlands Pharmacovigilance Centre Lareb received five reports of patients with RA with pustular psoriasis in association with the use of adalimumab (Humira®) until April 2, 2009.

Table 1. Reports of pustular psoriasis with the use of adalimumab.

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 62472, F, 77	adalimumab 40 mg once every 2 weeks, rheumatoid arthritis	alfacalcidol 0.25 μ g, methotrexate 2.5 mg, folic acid 0.5 mg	psoriasis pustular (palmaris et plantaris)	42 months, action taken with adalimumab and outcome unknown
B 68024 and 70659, M, 64	adalimumab, rheumatoid arthritis	omeprazole 20 mg, salazopyrine 2000 mg	extensive pustular psoriasis on the hands, feet and legs	13.5 months, adalimumab was withdrawn, 1 month later the patient had not yet recovered
C 78505, F, 39	adalimumab 40 mg once every 2 weeks, rheumatoid arthritis		psoriasis pustular plantaris palmaris	3.5 months, adalimumab was withdrawn, patient not yet recovered. Patient is treated with cutaneous tar preparations, corticosteroids, PUVA and acitretin

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
D 81015, F, 77	adalimumab 40 mg, rheumatoid arthritis	Folic acid 10 mg/week, methotrexate 7.5 mg	psoriasis pustular	1 month, adalimumab was withdrawn, patient was treated with methotrexate, tar, acitretin and recovered with sequel
E 78316 F, unknown age	adalimumab 40 mg, rheumatoid arthritis		acute severe pustular psoriasis	months, adalimumab was withdrawn, the patient was hospitalized and treated with prednisolone, ciclosporin and methotrexate. The pustular psoriasis improved.

Other sources of information

Literature

Pustular psoriasis is a rare and serious form of psoriasis consisting of widespread pustules on an erythematous background and systemic symptoms. Cutaneous lesions characteristic of psoriasis vulgaris may be present before, during, or after an acute pustular episode [2]. Palmoplantar psoriasis is a subtype of localized psoriasis that affects the palms of the hands and the soles of the feet. When it occurs without other psoriatic lesions, some consider it as a separate entity of unknown origin.

Among hypersensitivity reactions during TNF- α inhibitors like local reactions at the injection site, urticaria and other drug eruptions, also paradoxically, the development or exacerbation of psoriasis or psoriasis-like lesions have been reported [3,4,5]. This also includes pustular psoriasis, which most often is localized to the palms and soles [6]. In literature, (pustular) psoriasis is described as a class-effect of TNF-inhibitors [7,8,9].

Heymann in a review article on TNF-inhibitors and pustular psoriasis concludes that the majority of reported cases appeared in patients without a history of psoriasis, for whom the drug was administered for other conditions, most commonly RA [4]. Most cases, but not all, appear in women and there appears to be a predilection for the palms and soles.

In a prospective cohort study Flendrie *et al.* [10] focused on dermatologic complications in patients with 289 RA receiving anti-TNF- α therapy (follow-up period 2,3 years) with infliximab, etanercept, or adalimumab. They were compared with a group of 289 RA patients naïve to anti-TNF- α therapy. A significant greater number of dermatologic consultations (25%) was found, compared with the control group (13%), resulting in withdrawal of TNF- α therapy in 6,5% of patients.

De Gannes *et al.* observed new-onset psoriasis (n=13) or severe exacerbation of psoriasis (n=2) in 15 patients with a variety of rheumatologic conditions, during treatment with etanercept (n=6), infliximab (n=5), adalimumab (n=4) [8].

Wollina *et al.* reviewed 114 patients from the literature with (pustular) psoriasis and included six new patients (three women and three men) who developed pustular lesions during treatment with TNF- α inhibitors [9]. Palmoplantar pustular psoriasis occurred in 37 of the cases. A positive personal or family history of psoriasis was present in 25, respectively 8 patients. Timing of the occurrence of skin lesions varied considerable among the patients ranging from after a single application up to 63 months after initiation of therapy [9].

Beuthien *et al.* [5] describe the case of a 63-year-old female with a history of rheumatoid arthritis in which adalimumab was added to her regimen of methotrexate and leflunomide. Within a few hours of the sixth injection of adalimumab (at approximately week 12), she developed papulopustular lesions at the injection site on the thigh and on the palms and soles. This was followed by desquamation at these sites. There was no mucous membrane involvement. Adalimumab was discontinued and the eruption improved.

On the other hand, TNF- α inhibitors have been reported to be successful in pustular psoriasis; for example adalimumab effectively controlled recalcitrant generalized pustular psoriasis in an adolescent [4].

Databases

On April 02, 2009, the association of pustular psoriasis with the use of adalimumab was disproportionally present in the Lareb database with a ROR of 674 (95% CI = 192.5 - 2360.4).

The WHO database contained 141 cases of psoriasis (ROR 7.9, 95% CI = 6.6 - 9.4) but did not specify cases of pustular psoriasis.

On April 15, 2009, the Eudravigilance database contained 41 reports of pustular psoriasis in adalimumab users. The reaction was rated serious in all but two cases, and included 18 male patients and 22 female patients. Gender was not specified in one case; age ranged from 28 to 77 years. No reactions led to death or life-threatening disorders. Hospitalisation was necessary in fifteen cases, in three reports the reaction led to disability.

Mechanism

According to Collamer *et al.* the pathogenesis of psoriasis as an adverse drug reaction on TNF- α inhibitors appears to involve a disruption in cytokine balance following TNF inhibition, resulting in the up-regulation of plasmacytoid dendritic cells and the subsequent production of unopposed interferon-alpha, following a triggering event in predisposed individuals [11]. De Gannes *et al.* propose that cross regulation between TNF and type 1 interferon (IFN) may have a role in the pathogenesis of this reaction. This may result in pustular cutaneous inflammation. [8].

Discussion and conclusion

In total there are only ten reports of pustular psoriasis in the Lareb database. Five reports of pustular psoriasis concern the use of adalimumab (not including one duplicate report), all patients with RA. RA can be considered a prototype for the diseases characterized by neutrophilic inflammation, a feature it shares with psoriasis. This supports the role of dysregulation in cytokine balance, induced by TNF- α inhibitors. In the Lareb data base, there are also two reports of pustular psoriasis concerning the use of etanercept. In the SmPC of etanercept psoriasis is mentioned, but not pustular psoriasis [12]. Furthermore pustular psoriasis has been reported once with the use of metoprolol and amitriptyline. The association between adalimumab and pustular psoriasis is disproportionally present in the Lareb database and is also extensively described in the literature. Although

psoriasis is mentioned in the SmPC, (palmoplantar) pustular psoriasis as a specific subtype of psoriasis should also be explicitly mentioned.

- Pustular psoriasis should be mentioned in the SmPC of adalimumab

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