1.1. ACE-inhibitors and flushing

Introduction

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®), captopril, cilazapril (Vascase®), enalapril (Renitec®), fosinopril, 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.

Flushing may be defined as a sensation of warmth accompanied by visible reddening of the skin. Flushing is usually most prominent in the classic “blush area”, which includes the face, neck upper portion of the chest and upper limbs [1]. More or less similar or closely related reactions are blushing and hot flushes. Blushing is defined as involuntary reddening, especially of the face, associated with feelings of embarrassment, confusion or shame [2]. Hot flushes are described as a sudden, temporary sensation of heat predominantly experienced by some women during menopause [2].

The SmPCs of benazepril and ramipril mention (excessive) blushing as a possible adverse drug reaction, whereas the SmPCs of captopril and enalapril mention redness of the skin and redness of the face respectively. The SmPCs of fosinopril and trandolapril describe hot flushes. In the SmPC of zofenopril, a remark upon flushing with ACE-inhibitors in general can be found in the vascular section of the chapter adverse reactions. The SmPCs of the other ACE-inhibitors do not mention flushing, blushing, redness or hot flushes [3-13].

Reports

On April 13 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained fifteen reports of flushing and five reports of hot flushes in association with ACE-inhibitors (Table 1). Most of the flushing reports refer to (transient) redness in the facial area, but in patient F redness of the whole body is observed. In patients G and J flushing is accompanied by sweating. In several patients flushing is accompanied by other symptoms, including nausea and dizziness. Besides flushing, patient D also suffered from dizziness, substernal chest pain, dyspnoea and hypotension one hour after start of captopril; an anaphylactic reaction should be considered as underlying mechanism. In most cases the reported latency varied between one hour and several days after start of the drug. Six patients (J, L, N, O, Q and T) recovered after discontinuation of the suspected ACE-inhibitor. In patient L flushing began hours after starting fosinopril 10 mg once daily. Before, he used lisinopril without problems. After discontinuation of fosinopril he switched back to lisinopril and the symptoms of flushing disappeared. Patient O suffered from flushing within days after starting enalapril 10 mg once daily. He recovered after discontinuation of enalapril and switching to an angiotensin-II antagonist. In patient Q flushing, malaise, chest pain, increase in blood pressure and dysuria started several days after switching from Tritace® 5 mg twice daily to ramipril Sandoz 10 mg once daily. Ramipril was discontinued and enalapril with hydrochlorothiazide was prescribed (in a foreign country), resulting in recovery of symptoms. Patient T experienced flushing and metamorphopsia hours after drug substitution from lisinopril CF to lisinopril Accord. The symptoms diminished after dose reduction and disappeared after discontinuation. In all other patients the outcome is unknown.

Several patients used concomitant medications, which could also result in flushing. Among these are calciumantagonists (L, T) and vasodilators (L); both patients however experienced symptoms within hours after the suspected ACE-inhibitor and recovered after discontinuation.

Table 1. Reports of flushing and hot flushes with the use of ACE-inhibitors

Patient, Number, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome

Patient, Number, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 39 F, 68	enalapril 20mg o.d.		gastro-intestinal disorder nos, flushing	1 day discontinued not reported
B 1153 F, unknown	captopril 50mg o.d.	carbasalate calcium	dizziness, hot flushes	1 hour unknown not reported
C 1418 F, Unknown	lisinopril 2.5 mg o.d.		sweating increased, hot flushes	16 weeks unknown not reported
D 3722 M, unknown	captopril 25mg b.i.d.		dizziness, chest pain substernal, hot flushes, dyspnoea, hypotension nos	1 hour unknown not reported
E 9012 M, unknown	quinapril tablet 10mg o.d. primary hypertension	levothyroxine amiloride/hydrochlorothiazide metoprolol chlordiazepoxide	flushing	1 day discontinued not reported
F 13206 F, 49	lisinopril 20mg o.d. primary hypertension		nausea, sweating increased, flushing	2 hours discontinued not reported
G 13631 M, 76	enalapril 10mg o.d. primary hypertension	cimetidine nitrazepam oxazepam	flushing	2 hours no change not reported
H 14511 M, 71	enalapril 20mg o.d.	digoxine acetylsalicylic acid amoxicillin	hot flushes	1 week unknown not reported
I 14576 F, 58	captopril 25mg o.d.	amiloride//hydrochlorothiazide	flushing	1 year no change not reported
J 15377 M, 38	lisinopril 10mg o.d primary hypertension	atenolol paroxetin multivitamin complex	headache, heart pounding, flushing	2 days discontinued recovered
K 23669 F, 61	enalapril 5mg o.d. primary hypertension	estradiol hydrochloro-thiazide medroxy-progesterone	flushing	hours discontinued not reported
L 31768 M, 48	fosinopril 10mg o.d. heart failure	metoprolol diltiazem omeprazole acetylsalicylic acid isosorbidedinitrate naproxen	flushing	hours discontinued recovered
M 33432 M, 56	enalapril 10mg o.d. primary hypertension		sleeplessness, tinnitus, hot flushes	3 days no change unknown
N 41380 M, unknown	zofenopril 7,5mg b.i.d. primary hypertension	furosemide atorvastatin sotalol clopidogrel	insomnia, flushing	1 hour discontinued recovered

Patient, Number, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
O 42141 M, 57	enalapril 10mg o.d. metformin 500mg o.d. non-insulin-dependent diabetes mellitus	betaxolol eyedrops	flushing	days discontinued recovered
P 63530 F, 83	enalapril 20mg o.d. hypertension	levothyroxine glimepiride	redness facial, flushing	minutes no change unknown
Q 64934 M, 57	ramipril Sandoz 10mg o.d.		therapeutic response unexpected with drug substitution, malaise, chest pain, hypertension aggravated, dysuria, flushing	5 days discontinued recovered
R 76591 M, 69	perindopril 8 mg. o.d. hypertension gliclazide 80 mg t.i.d. diabetes mellitus, dipyridamol 200mg b.i.d. CVA hydrochloorthiazide 25mg o.d. metformine 850mg t.i.d. diabetes mellitus, acetylsalicylic acid 80mg o.d. CVA		pruritus, diarrhea, appetite lost, nausea, flushing	2 month unknown unknown
S 78867 F, 4	enalapril 5mg proteinuria oxybutynine 2,5mg t.i.d. overactive bladder	ferrofumarate	flushing aggravated	9 months no change unknown
T 90524 M, 67	lisinopril Accord 5mg o.d. hypertension	furosemide verapamil digoxin pravastatin phenprocoumon	therapeutic response unexpected with drug substitution, metamorphopsia, flushing	hours discontinued recovered

Other sources of information

SmPC

The Dutch SmPCs of benazepril, ramipril, captopril, enalapril, fosinopril, trandolapril and zofenopril mention either blushing, (facial)redness, flushing or hot flushes. The SmPCs of the other ACE-inhibitors mention neither of these symptoms [3-13]. However, in the US SmPC of lisinopril flushing is described [14].

Literature

ACE-inhibitors are mentioned as one of the medication groups that have been associated with flushing [1]. Flushing is mentioned as one of the side effects of ACE-inhibitors in Meylers' Side Effect of drugs [15]. Flushing was associated with enalapril previously in a case report [16]. This patient complained of sustained intense flushing and warmth predominantly of the face and neck, two weeks after the start of enalapril. The 24-hour urine 5-hydroxyindoleatic acid level (for detection of metastatic carcinoid tumors) was normal. With the discontinuation of enalapril therapy, the flushing resolved within 48 hours. Re-challenge with enalapril produced flushing within four hours after the first dose.

Databases

On April14 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained fifteen cases of flushing and five cases of hot flushes in association with ACE-inhibitors. For flushing, the ROR was neither statistically disproportional for the individual ACE-inhibitors, nor for the ACE-inhibitors as a group (ROR=1.63, 95% CI: 0.97 - 2.74). For hot flushes, the ROR for the group ACE-inhibitors was 0.7 (95 % CI: 0.29 - 1.70).

The database of the World Health Organization contained 174 reports of flushes associated with the use of ACE-inhibitors and 138 cases of hot flushes. The reporting odds ratio (ROR) for either association was not statistically disproportional.

On April 12 the Eudravigilance database contained 61 cases of ACE-inhibitor associated flushing affecting 38 female patients and 21 male patients. All but seven cases were rated serious. Hospital admission was reported 26 times. In these cases flushing was mostly part of a more extended reaction (hypersensitivity or hypotension). In 25 cases the seriousness criteria "Other" was completed. The patients' gender was not specified in two reports. Ages ranged from 14 to 84 years. Ten reports concerned women between 45 and 60 years old.

Hot flushes were reported fifteen times. In four cases perimenopausal symptoms could not be ruled out due to ages between 45 and 60 years. Patients involved ranged in age from 33 to 88 years, and were predominantly female (11 cases), in one case no gender was specified and three patients were men; one was treated for prostate carcinoma, in one man flushing was part of an extensive reaction with respiratory insufficiency and in one men flushing began after a combination of an ACE inhibitor and Angiotensin II antagonist. Eleven cases were rated serious. In six cases this was due to other reasons or not indicated. In six cases the reaction led to hospital admission (in one of these cases the reaction was part of a life threatening condition).

Prescription data

The increasing number of patients using ACE-inhibitors is shown in Table 2 [17].

Table 2. Number of ACE inhibitors users in the Netherlands between 2005 and 2008

Drug	2005	2006	2007	2008
C09AA ACE-inhibitors	714,490	809,590	805,110	897,390

Mechanism

ACE-inhibitors are competitive inhibitors of angiotensin-converting enzyme (also known as kininase II). ACE inhibitor administration results in significantly decreased plasma concentrations of angiotensin II and decreased plasma aldosterone concentrations (and increased concentrations of angiotensin I).
Angiotensin converting enzyme is also responsible for the degradation of bradykinin, a naturally occurring vasodilator. There is some evidence to show that ACE-inhibitors are responsible for the inhibition of this pathway leading to an accumulation of bradykinin. Bradykinin enhances the

production of vasodilators, including endothelium derived relaxing factor (EDRF = NO = nitrogen monoxide) and prostaglandin (PG) E2 and I2 [16,18]. Recent studies show that bradykinin stimulates epoxyeicosatrienoic acid release. Epoxyeicosatrienoic acids are cytochrome P450 epoxygenase metabolites of arachidonic acid. They are synthesized by the vascular endothelium and open calcium-activated potassium channels, hyperpolarize the membrane, and relax vascular smooth muscle, resulting in vasodilation, independently of NO and PG production [19,20].
Cutaneous vasodilation results in an increased skin temperature and redness. Flushing therefore is an adverse reaction, which can be directly related to the pharmacological effect of many vasodilator drugs, including calcium antagonists and nitrates.

Conclusion

The Lareb database contains 15 reports of flushing and 5 reports of hot flushes in association with ACE-inhibitors. In seven out of eleven Dutch SmPCs of ACE-inhibitors flushing or comparable descriptions, including blushing, hot flushes or (facial) redness of the skin is mentioned. This association is supported by the literature and possible mechanism of action of ACE-inhibitors.
It should be considered to mention flushing in the SmPCs of all ACE-inhibitors.

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This signal has been raised on September 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).