1.1. ACE-inhibitors and nightmares or abnormal dreaming

Introduction

In a previous quarterly report (2009-2) the association between AT_1 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
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

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
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 for trandolapril (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)
	Lareb database		*WHO database*	
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 AT_1 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 AT_1 receptor antagonists [17]. However, Lareb received 16 reports of abnormal dreaming or nightmares associated with the use of AT_1 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 lipophility of the drugs. AT_1 receptor antagonists have a higher lipophility 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 lipophility [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.

References

1. Pagel JF, Helfter P. Drug induced nightmares-an etiology based review. Hum Psychopharmacol 2003;18(1):59-67.
2. Dutch SPC Renitec®. (version date: 3-8-2009, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h10575.pdf.
3. Dutch SPC Cibacen®. (version date: 31-3-2009, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h14079.pdf.
4. Dutch SPC captopril Apotex. (version date: 1-3-2009, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h19987.pdf.
5. Dutch SPC Vascase®. (version date: 1-12-2008, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h15132.pdf.
6. Dutch SPC Newace®. (version date: 20-5-2009, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h15237.pdf.
7. Dutch SPC Zestril®. (version date: 11-6-2009, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h12560.pdf.
8. Dutch SPC Coversyl®. (version date: 13-3-2009, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h13635.pdf.
9. Dutch SPC Acupril®. (version date: 23-7-2009, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h13601.pdf.
10. Dutch SPC Tritace®. (version date: 21-8-2006, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h13294.pdf.
11. Dutch SPC Gopten®. (version date: 7-7-2007, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h15860.pdf.
12. Dutch SPC Zofil®. (version date: 24-3-2004, access date: 31-8-2009) http://db.cbg-meb.nl/IB-teksten/h23720-h23721-h23722-h23723.pdf.
13. Haffner CA, Smith BS, Pepper C. Hallucinations as an adverse effect of angiotensin converting enzyme inhibition. Postgrad Med J 1993;69(809):240
14. Pagel JF. Nightmares and disorders of dreaming. Am Fam Physician 2000;61(7):2037-42, 2044.

15. College for health insurances. GIP database. (version date: 9-6-2009, access date: 31-8-2009) http://www.gipdatabank.nl/.
16. Thompson DF, Pierce DR. Drug-induced nightmares. Ann Pharmacother 1999;33(1):93-8.
17. Novak M, Shapiro CM. Drug-induced sleep disturbances. Focus on nonpsychotropic medications. Drug Saf 1997;16(2):133-49.
18. Saavedra JM, Benicky J, Zhou J. Angiotensin II: multitasking in the brain. J Hypertens Suppl 2006;24(1):S131-S137
19. Saavedra JM. Brain angiotensin II: new developments, unanswered questions and therapeutic opportunities. Cell Mol Neurobiol 2005;25(3-4):485-512.
20. Seltzer A, Bregonzio C, Armando I, Baiardi G, Saavedra JM. Oral administration of an AT1 receptor antagonist prevents the central effects of angiotensin II in spontaneously hypertensive rats. Brain Res 2004;1028(1):9-18.
21. Saavedra JM, Armando I, Bregonzio C, Juorio A, Macova M, Pavel J, Sanchez-Lemus E. A centrally acting, anxiolytic angiotensin II AT1 receptor antagonist prevents the isolation stress-induced decrease in cortical CRF1 receptor and benzodiazepine binding. Neuropsychopharmacology 2006;31(6):1123-34.
22. Gvilia I, Angara C, McGinty D, Szymusiak R. Different neuronal populations of the rat median preoptic nucleus express c-fos during sleep and in response to hypertonic saline or angiotensin-II. J Physiol 2005;569(Pt 2):587-99.
23. University of Alberta, Canada. DrugBank. (access date: 31-8-2009) http://www.drugbank.ca/.

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