1.1. Angiotensin II AT_1 receptor antagonists and nightmares or abnormal dreaming

Angiotensine II AT_1 receptor antagonists are registered in the Netherlands for the treatment of hypertension, heart failure, nephropathy in patients with hypertension and diabetes mellitus type 2 and reduction of cardiovascular morbidity and mortality in patients with left ventricular hypertrophy. Since 1995 the following AT_1 receptor antagonists have been registered in the Netherlands: losartan (Cozaar®), valsartan (Diovan®), telmisartan (Micardis®), olmesartan (Olmetec®), irbesartan (Aprovel®), eprosartan (Teveten®) and candesartan (Atacand®) [1-7]. For most AT_1 receptor antagonists combinations with other antihypertensive drugs are registered.
A nightmare is defined by the DSM IV criteria as a frightening dream. Clinically the most common definition for nightmare is an unpleasant or frightening dream usually occurring in REM sleep (American Academy of Sleep Medicine) [8].
The SmPC of the losartan/hydrochlorothiazide combination mentions sleep disturbances and abnormal dreaming [9]. Nightmares or abnormal dreams are not mentioned in all other SmPCs of AT_1 receptor antagonists containing products currently marketed in the Netherlands. Some SmPCs mention sleep disturbances [1,10] or insomnia [2,7,10,11].
The current report describes nightmares or abnormal dreaming associated with the use of AT_1 receptor antagonists.

Reports

On 15 February 2009, the Netherlands Pharmacovigilance Centre Lareb had received 16 reports of nightmares or abnormal dreaming associated with AT_1 receptor antagonists (see Table 1). Seven reports concerned losartan, four valsartan, three telmisartan and two irbesartan. In 10 patients nightmares or abnormal dreaming started within one day after treatment with AT_1 receptor antagonists, in three patients within one week, and in two patients after more than one week. For one patient latency was not reported. The cases were reported by eight pharmacists, seven GPs and one consumer.
The AT_1 receptor antagonists were withdrawn in nine patients: seven recovered and in two patients the outcome was unknown. In six patients therapy was continued: two recovered, two did not recover and in two patients the outcome was not reported. In one patient we had no information about drug withdrawal.
Two patients using valsartan reported a positive rechallenge. Patient H experienced nightmares one day after start of therapy. He had also experienced nightmares the previous time he had used valsartan. Patient I had experienced nightmares since the start of the therapy. She stopped on her own initiative because of the nightmares, and recovered. After restart she experienced nightmares again.
Seven patients used a β-blocker as co-medication, and in two patients a statin was used, which have been associated with nightmares previously [12,13].

Table 1. Reports of nightmares or abnormal dreaming associated with use of AT_1 receptor antagonists.

Patient, Sex, Age	Drug, Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 17386 F, 66	losartan 50mg, primary hypertension	levothyroxine formoterol aerosol acetylsalicylic acid temazepam	hallucination, abnormal dreaming	1 day discontinued recovered
B 16390 F, 70	losartan 50mg, primary hypertension	amiloride	nightmares	2 days discontinued recovered
C 38675 F, age not reported	losartan 50mg, primary hypertension		abnormal dreaming, apathy, fatigue	hours discontinued recovered

D 21914 M, 77	losartan 50mg triamterene/HCT 50/25mg	furosemide acebutolol epoetin	abnormal dreaming: 'unpleasant dreams'	not reported no change not reported
E 42175 F, age not reported	losartan 50mg furosemide 250mg	sotalol nifedipine enalapril, atenolol paracetamol	excessive dreaming	hours no change not recovered
F 65223 F, 77	losartan 50mg, hypertension	carbasalate calcium metformin levothyroxine	abnormal dreaming	40 days discontinued unknown
G 80072 F, 75	losartan 50mg, primary hypertension	chlorthalidone	excessive dreaming, sleep restless,	1 day no change recovered
H 74207 M, 76	valsartan 80mg, hypertension		nightmares	1 day discontinued recovered
I 34409 F, age not reported	valsartan 80mg,	carbasalate calcium temazepam simvastatin beclomethasone inhalation psyllium seeds alendronate	nightmares	1 day discontinued recovered
J 66592 F, 78	valsartan 80mg, prevention	epoetin bisoprolol omeprazole flecainide amlodipine carbasalate calcium isosorbide mononitrate furosemide	nightmares, arthralgia	4 years discontinued recovered
K 71840 F, 86	valsartan 80mg, hypertension		nightmares	6 days no change recovered
L 51059 F, 62	telmisartan 20mg, hypertension	hydrochloro-thiazide metoprolol	nightmares, panic reaction, headache	3 days discontinued not reported
M 50316 F, 77	telmisartan 80mg, hypertension	perindorpil/HCT sotalol fenprocoumon isosorbide dinitrate	abnormal dreaming, hallucination, vision blurred, hypotension	1 day discontinued recovered
N 40734 F, age not reported	telmisartan 80mg	metoprolol temazepam simvastatin carbasalate calcium	nightmares, somnolence, scaly rash	1 day discontinued unknown
O 49741 M, 55	irbesartan/HCT 300/12,5mg amlodipine, hypertension	budesonide inhalation	excessive dreaming	1 day no change not recovered
P 79276 M, 71	irbesartan 300mg atorvastatin 10mg acetylsalicylic acid 80mg		nightmare	1 day unknown not recovered

Other sources of information

SmPC

The American SmPC of losartan mentions abnormal dreaming as potentially important event that occurred. It could not be determined whether causality was related to losartan [14].

Literature

Nightmares are related to an increased intensity of REM sleep [15]. 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]. Also nightmares may occur when drugs that cause REM sleep rebound are withdrawn [17]. Nightmares or abnormal dreaming were associated with ACE inhibitors (captopril, enalapril and quinapril) and losartan in case-reports and a reviews [8,18,19].

Databases

On February 19 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained eight cases of nightmares associated with AT_1 receptor antagonists use. A case non-case comparison showed that reports of AT_1 receptor antagonists and nightmares were not disproportionally present in the database, with a reporting odds ratio (ROR) of 1.2 (95% CI=0.60-2.5). The same association was disproportional in the database of the World Health Organisation for adverse drug reactions with a total of 82 cases and a ROR of 1.7 (95% CI=1.4-2.1). The number of reports of the separate drugs, and their ROR calculated on both the Lareb database as the WHO database are presented in Table 2.
On February 19 2009, the Lareb database had seven reports of abnormal dreaming associated with AT_1 receptor antagonists use. This number was not disproportional (ROR=1.6, CI=0.7-3.5). The number of 40 cases in the WHO database was disproportional (ROR=1.5, 95% CI=1.1-2.1). The number of reports of the separate drugs are presented in Table 3. No disproportionality analysis was made for combinations of AT_1 receptor antagonists with other drugs.

Table 2. Number of reports on nightmares associated with AT_1 receptor antagonists 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*[*]	
losartan	1		25	1.6 [1.1 - 2.5]
valsartan	4	3.6 [1.3 - 9.7]	14	1.3 [0.76 - 2.2]
telmisartan	2		11	2.0 [1.1 - 3.7]
irbesartan	1		16	1.3 [1.01-1.7]
candesartan			11	1.1 [0.86-1.5]
olmesartan			4	0.94 [0.60-1.5]
eprosartan			1	-
total	**8**	**1.2 [0.6 - 2.5]**	**82**	**1.7 [1.4-2.1]**

*In the WHO database nightmares are covered by the WHOart-term paroniria.

Table 3. Number of reports on abnormal dreaming associated with AT_1 receptor antagonists 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)

Drug	Number of reports	ROR (95% CI)	Number of reports	ROR (95% CI)
	Lareb database		*WHO Database*	
losartan	6	3.4 [1.5 - 7.7]	15	1.2 [0.98-1.5]
valsartan			2	
telmisartan	1			
irbesartan			11	1.3 [1.01-1.7]
candesartan			9	1.1 [0.86-1.5]
olmesartan				
eprosartan			3	1.5 [0.89-2.5]
total	**7**	**1.6 [0.7 - 3.5]**	**40**	**1.5 [1.1-2.1]**

Prescription data

In 2007, AT_1 receptor antagonists were used by 519,520 patients The number of users of the specific drugs is shown in Table 4. In 2007, combinations of AT_1 receptor antagonists with other antihypertensive drugs were used by 238,630 patients.

Table 4. Number of users of AT_1 receptor antagonists in the Netherlands between 2003 and 2007 (Source: GIP-databank).

	2003	2004	2005	2006	2007
losartan	135,650	150,090	158,860	187,320	187,010
valsartan	63,234	75,354	84,081	107,130	116,350
irbesartan	63,800	79,738	89,966	113,230	113,750
candesartan	41,057	44,878	48,746	59,897	59,021
telmisartan	14,530	20,637	22,850	29,870	31,739
olmesartan	.	3,830	5,571	9,156	13,349
eprosartan	5,617	8,817	9,508	8,575	7,071

Mechanism

In addition to functions such as controlling systemic blood pressure, angiotensin II has several roles in the brain [20]. 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 [21]. A recent review about the central effects of angiotensin II shows that central AT_1 antagonism can be considered as a therapeutic approach in brain ischemia and stress-related mood disorders [21]. Spontaneous hypertensive rats express a greater number of endothelial AT_1 receptors and a central sympathic overdrive, and central AT_1 antagonism with candesartan reversed these effects [20]. Also, angiotensin II seemed involved in higher regulatory mechanisms controlling responses to stress and anxiety: antagonism of brain angiotensin II with candesartan could block angiotensin II induced stress and anxiety in rats [22,23].
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 [24].

Discussion and conclusion

Animal studies have shown a role for angiotensin in the brain [20], and Lareb has published a quarterly report about psychiatric adverse drug reactions in losartan in 2005 [25]. In one animal study, it was shown that angiotensin II reduced REM sleep [24], hence it is possible that blocking AT_1 receptors may stimulate REM sleep, and induce nightmares or abnormal dreaming.

The Netherlands Pharmacovigilance Centre Lareb received 16 reports of nightmares or abnormal dreams associated with AT_1 receptor antagonists. The short latency in most patients, the nine patients recovering after withdrawal, and two patients experiencing a positive rechallenge are supportive for a causal relationship. The relation was disproportionally present in the WHO database of adverse drug reactions, and the association was mentioned in reviews about drug-induced nightmares. Although no pharmacological mechanism has been proved in humans, animal studies have shown a role for angiotensin in the brain in relation to REM sleep. Nightmares and abnormal dreaming should be mentioned in the SmPCs of all AT_1 receptor antagonists.

References

1. Dutch SmPC of losartan (Cozaar®). (version date: 4-12-2008, access date: 9-2-2009) db.cbg-meb.nl/IB-teksten/h17617.pdf.
2. European SmPC of telmisartan (Micardis®). (version date: 16-12-2008, access date: 9-2-2009) http://www.emea.europa.eu/humandocs/Humans/EPAR/micardis/micardis.htm.
3. Dutch SmPC of valsartan (Diovan®). (version date: 7-1-2009, access date: 9-2-2009) http://db.cbg-meb.nl/IB-teksten/h26939.pdf.
4. Dutch SmPC of olmesartan (Olmetec®). (version date: 27-5-2003, access date: 9-2-2009) http://db.cbg-meb.nl/IB-teksten/h28782.pdf.
5. European SmPC of irbesartan (Aprovel®). (version date: 28-8-2008, access date: 9-2-2009) http://www.emea.europa.eu/humandocs/PDFs/EPAR/Aprovel/H-141-PI-nl.pdf.
6. Dutch SmPC of eprosartan (Teveten®). (version date: 14-1-2008, access date: 9-2-2009) http://db.cbg-meb.nl/IB-teksten/h22260.pdf.
7. Dutch SmPC of candesartan (Atacand®). (version date: 2-10-2007, access date: 9-2-2009) http://db.cbg-meb.nl/IB-teksten/h21703.pdf.
8. Pagel JF, Helfter P. Drug induced nightmares--an etiology based review. Hum.Psychopharmacol. 2003;18(1):59-67.
9. Dutch SmPC of losartan/hydrochlorothiazide (Hyzaar®). (version date: 4-12-2008, access date: 9-2-2009) http://db.cbg-meb.nl/IB-teksten/h19269.pdf.
10. Dutch SmPC of valsartan/hydrochlorothiazide (Co-Diovan®). (version date: 7-1-2009, access date: 9-2-2009) http://db.cbg-meb.nl/IB-teksten/h22365.pdf.
11. European SmPC of irbesartan/hydrochlorothiazide (CoAprovel®). (version date: 1-10-2008, access date: 9-2-2009) http://www.emea.europa.eu/humandocs/PDFs/EPAR/Coaprovel/H-222-PI-nl.pdf.
12. Thompson DF, Pierce DR. Drug-induced nightmares. Ann Pharmacother 1999;33(1):93-8.
13. HMG-CoA-reductase inhibitors and nightmares or abnormal dreaming. Lareb Quarterly Report 2008;(3):9-15.
14. American SmPC of losartan (Cozaar®). (version date: 1-3-2001, access date: 20-2-2009) http://www.fda.gov/cder/foi/label/2001/20386s26lbl.pdf.
15. Pagel JF. Nightmares and disorders of dreaming. Am Fam Physician. 2000;61(7):2037-42, 2044.
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. Haffner CA, Smith BS, Pepper C. Hallucinations as an adverse effect of angiotensin converting enzyme inhibition. Postgrad Med J 1993;69(809):240.
19. Thompson DF, Pierce DR. Drug-induced nightmares. Ann Pharmacother. 1999;33(1):93-8.
20. Saavedra JM, Benicky J, Zhou J. Angiotensin II: multitasking in the brain. J Hypertens Suppl 2006;24(1):S131-S137.
21. Saavedra JM. Brain angiotensin II: new developments, unanswered questions and therapeutic opportunities. Cell Mol.Neurobiol. 2005;25(3-4):485-512.
22. 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.
23. 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.
24. 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.
25. Losartan and psychiatric adverse drug reaction. Lareb Quarterly Report 2005;(4):18-20.

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