CASE REPORT

Lisinopril-Induced Nightmares

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Drug-induced nightmares have been reported in the literature and are a known adverse effect of certain antihypertensive agents such as α-agonists and β-blockers. Data are limited, however, on the association of this adverse effect with angiotensin-converting enzyme (ACE) inhibitors. We describe a 63-year-old, obese woman, with no history of illicit drug abuse, alcohol abuse, or psychiatric illness, who developed nightmares after starting lisinopril 10 mg/day for blood pressure control. The drug was discontinued, triamterene-hydrochlorothiazide was started, and her nightmares ceased. One year later, the patient continued to have no complaints of nightmares. At that time, however, her blood pressure was slightly elevated. Triamterene was discontinued, and lisinopril was restarted at a lower dose of 5 mg/day, in addition to hydrochlorothiazide 25 mg/day. Her nightmares returned; however, the patient decided to continue taking the lisinopril and tolerate the nightmares. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 6) between the patient's development of nightmares and lisinopril therapy. The exact mechanism by which ACE inhibitors cause this drug reaction is not known. Clinicians should be aware of this potential adverse effect when monitoring patients receiving ACE inhibitors.

Key Words: ACE inhibitor, angiotensin receptor blocker, nightmares, dreams, hypertension, sleep disorders, lisinopril.

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Drug-induced nightmares have been reported in clinical trials as well as in case reports for several drugs including dopamine agonists, anticholinergics, benzodiazepines, tricyclic antidepressants, and β-blockers.[1, 2] Some drugs are known to cause neurochemical imbalances and thus lead to nightmares; however, for other drugs, the mechanism of this adverse effect is still not understood. Dopamine and norepinephrine, as well as serotonin and γ-aminobutyric acid, are the neurotransmitters thought to affect sleep. When patients receive drugs influencing these neurotransmitters, they may experience negative effects.[1] Another mechanism of this adverse effect may involve drugs affecting the central nervous system and adrenergic receptors, which have been known to influence rapid eye movement (REM) sleep.[1]

β-Blockers are a class of antihypertensive agents that have been associated with nightmares.[1, 3] An association between angiotensin-converting enzyme (ACE) inhibitors and nightmares, however, has not been well documented, with only one case, to our knowledge, published in the literature.[4] This class of drugs, which exerts its effects by acting on the renin-angiotensin system, is widely used for the treatment of hypertension, heart failure, and other diseases. Well-known adverse effects of ACE inhibitors include cough, headache, and angioedema.[5] In this case report, we describe a woman who experienced nightmares while

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taking the ACE inhibitor lisinopril.

Case Report

A 63-year-old, obese woman went to her family medicine clinic for a routine visit. Her medical history was significant for hypertension, hyperlipidemia, and type 2 diabetes mellitus, and she had recently been tested for sleep apnea but the diagnosis had not been confirmed. She had no history of alcohol abuse, illicit drug use, or psychiatric illness. The patient had no drug allergies, and her drug therapy consisted of triamterene 37.5 mg–hydrochlorothiazide 25 mg/day and aspirin 81 mg/day. Her diabetes was controlled with lifestyle modifications.

At this visit, the patient's body mass index was 47 kg/m^2 and blood pressure was 137/76 mm Hg. Laboratory test results revealed a hemoglobin A_{1c} of 7.0% (normal < 7%), serum creatinine concentration 0.8 mg/dl (0.5–1.3 mg/dl), potassium 4.0 mEq/L (3.6–5.0 mEq/L), and low-density lipoprotein cholesterol (LDL) 134 mg/dl (target < 100 mg/dl). The patient was prescribed lisinopril 10 mg/day for blood pressure control and renal protection, along with pravastatin 40 mg/day for her elevated LDL level. Triamterene-hydrochlorothiazide was discontinued.

Two weeks later, the patient returned to the clinic for a follow-up appointment and complained of disturbing nightmares that had begun immediately after starting the new drugs. The nightmares she described included events such as being locked up in a box and finding her grandchildren severely injured. Lisinopril was discontinued, triamterene-hydrochlorothiazide was restarted, and the patient continued pravastatin. After these changes were made in her drug therapy, her nightmares stopped.

One year after the lisinopril had been discontinued, the patient continued to have no complaints of nightmares. Her blood pressure, however, remained slightly elevated at 132/88 mm Hg. Triamterene was discontinued, and lisinopril was restarted at a lower dose of 5 mg/day, in addition to hydrochlorothiazide 25 mg/day. Her nightmares returned; however, the patient elected to continue with the lisinopril despite this effect and tolerated the nightmares.

Discussion

Drug-induced nightmares are well documented; however, to our knowledge, only one other case report of nightmares associated with ACE inhibitor use has been published.[4] To further explore the association of nightmares with ACE inhibitor use, a MEDLINE search of the literature was performed. Search terms were drug-induced nightmares, ACE inhibitors and nightmares, antihypertensives and nightmares, and adverse effects of ACE inhibitors. The case report of ACE inhibitors associated with nightmares described disturbed visual perception and nightmares with the use of captopril, but the information provided was incomplete.[4] Another case report documented nightmares with use of an angiotensin II receptor blocker (ARB), which also acts on the renin-angiotensin system.[6] The authors of a review of drug-induced nightmares reported that antihypertensive agents affect adrenergic receptors in the central nervous system and can affect REM sleep and dreaming.[1] However, β-blockers and α-agonists are the most commonly reported antihypertensives to cause nightmares and account for approximately one third of all reported nightmare adverse events related to drug therapy.[1–3, 7] In one study, the frequency of nightmares was 5.8% with β-blockers, 2.0% with calcium channel blockers, and 1.4% with ACE inhibitors.[8]

Sleep disturbances are relatively common in the general population.[1–3, 7] A 1980 study found that women taking antihypertensive drugs had an increase in nightmares, and sleep disturbances in general, compared with the general population.[7] In this study, patients taking antihypertensive drugs reported sleep disturbances 38% of the time, compared with 33% in individuals not taking antihypertensive drugs. This difference was not significant, but the authors stated that their results suggest that although sleep-related adverse effects are infrequent, they may be associated with these drugs.

One potential mechanism of ACE inhibitor–induced nightmares is production of upper airway inflammation that possibly contributes to obstructive sleep apnea.[9–11] The association of ACE inhibitors with sleep apnea has been further tied to the sleep apnea causing nightmares.[9–11] However, these reports involved a small number of patients, and no general effect of sleep apnea has been observed on dream content. Although the clinical significance is unknown, ACE inhibitors may also cause insomnia and affect norepinephrine levels, which theoretically could lead to nightmares.[1]

In three clinical trials, abnormal dreaming was reported in patients receiving enalapril (0.5–1% of patients), losartan potassium (which was reported as an ACE inhibitor; ~1%), and quinapril (frequency not reported).[1] These adverse events, however, were not directly referenced in the report,

and a MEDLINE search did not reveal their findings. Adverse effects of ACE inhibitors were evaluated in another report, but the difference between the frequency of nightmares in users (5.2%) and nonusers (5.0%) was not significant.[12]

Another review described a patient who experienced nightmares after taking captopril; the authors used the Naranjo adverse drug reaction probability scale and determined a possible relationship between the drug and the adverse event.[2] The details of this case report revealed that this patient received captopril 12.5 mg 3 times/day and developed disturbed visual perceptions on rousing from sleep as well as nightmares.[4] Very little additional patient-specific or drug information, including the specific Naranjo score, was provided in this case report.

In the case of the patient who experienced nightmares after taking an ARB, they occurred within 1 week of starting valsartan 80 mg/day.[6] The patient stopped taking the drug, and the nightmares ceased. On rechallenge, the nightmares returned and again stopped when the valsartan was discontinued and quinapril (an ACE inhibitor)-hydrochlorothiazide was started.

Angiotensin-converting enzyme inhibitors have been prescribed as an alternative for patients who experience nightmares associated with the use of other antihypertensive agents. In a multicenter study, four patients who had nightmares while taking antihypertensive agents such as β-blockers or hydralazine reported improvement after changing to captopril, with dosages ranging from 12.5 mg once/day to 50 mg 3 times/day.[13]

Use of the Naranjo adverse drug reaction probability scale[14] in our patient indicated a probable relationship (score of 6) between the patient's development of nightmares and lisinopril therapy. As mentioned, only one other case report of nightmares associated with ACE inhibitor use (captopril) has been published,[4] as well as one with the use of an ARB (valsartan).[6] Although the report of this adverse effect with valsartan provides a good foundation for the likelihood of this adverse effect with ARBs, not enough information was provided in the captopril case report to determine causality. Although sleep apnea may contribute to the frequency of nightmares, we do not believe this to be the cause in our patient. Regardless of the mechanism, based on the strong correlation of lisinopril use with nightmare occurrence, which was confirmed on rechallenge, we believe that lisinopril induced our patient's nightmares.

Conclusion

We report a probable case of nightmares associated with lisinopril. As there is no established mechanism by which ACE inhibitors may cause nightmares, more research is needed. Clinicians should be aware of this potential adverse effect when monitoring patients receiving ACE inhibitors.

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