



Doctor, There's a Fly in my Soup! Angiotensin-Converting Enzyme Inhibitors, Endogenous Opioids and Visual Hallucinations

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We present a case of visual hallucinations related to initiation of angiotensin-converting enzyme inhibitor therapy. A short review of the literature follows, including a discussion of a proposed mechanism.

Patient Description

A 70 year old woman complaining of pain in her arm was examined one week after having fractured her right radius. She also reported that the previous day, while eating lunch, she had suddenly seen insects swarming in her soup and running up her spoon and into her mouth.

Two days previously she had begun anti-hypertensive therapy with cilazapril, 2.5 mg a day. Her other medications included omeprazole, 20 mg/day, that she had been taking for 5 years for esophagitis, and paracetamol and dipyron, which she took as needed for the pain in her arm since the fracture.

Eight years prior to this incident, the patient was treated for a low grade gastric lymphoma with a short course of chemotherapy and radiotherapy; there was no subsequent evidence of recurrence. No further history of illnesses, medications, substance abuse or visual hallucinations was elicited. Her blood pressure was 140/80.

She continued to take cilazapril. On repeat examination 2 weeks later, she reported that the pain had lessened. She also complained of periodically seeing a fly roaming the periphery of her vision.

Due to the temporal relationship of the visual hallucinations to the initiation of cilazapril therapy, we sought to determine if this was a known side effect of the drug.

Comment

Tarlow et al. [1] describe a case of vivid visual hallucinations in an elderly woman given quinapril for congestive heart failure 2 weeks after having fractured her hip [1]. The authors also cite three other cases of visual hallucinations described in the literature. The first involved a 73 year old man who was hospitalized with pulmonary edema 2 months after a myocardial infarction [1]. Enalapril therapy resulted in visual hallucinations in which the ward beds all vanished and the entire staff appeared pregnant. No hypotension occurred, and blood glucose and electrolyte levels were normal. The drug was discontinued and the hallucinations resolved. Three weeks later due to recurrent pulmonary edema, therapy with captopril at a dose of 12.5 mg three times daily was commenced. Within 24 hours his hallucinations returned in the form of insects running up and down the curtains. The hallucinations resolved a day after captopril was discontinued. The second case was a 64 year old man who developed heart failure 3 weeks after a myocardial infarction. Initiation of captopril therapy at a dosage of 12.5 mg three times daily resulted in visual hallucinations, always worse within 2 hours of taking captopril.

The drug was not discontinued owing to a significant improvement in his heart condition. The third case described visual hallucinations after initiation of quinapril in an elderly woman with symptomatic congestive heart failure. Another article [2] described confusion and hallucinations in a 76 year old man given captopril for severe heart failure. Reduction in dosage did not help, but intravenous naloxone completely restored mental functioning. It was suggested that captopril inhibited the enzyme enkephalin dipeptidyl carboxypeptidase, thus enhancing opioid activity. Further reports in the literature of hallucinations caused by enalapril or captopril are scarce. None were found implicating cilazapril.

Our patient experienced a visual hallucination 2 days after initiation of therapy with cilazapril. Do the five cases described above, and ours, have something in common, apart from the fact that all patients were on ACE-inhibitor therapy? We propose the following explanation: the substance directly responsible for the hallucinations in this patient was an endogenous opioid, the level of which was physiologically elevated in response to the pain caused by her fracture. It is known that the level of endogenous opioids increases in response to pain and other conditions, including acute heart failure [3] that necessitated the ACE-inhibitor therapy

ACE = angiotensin-converting enzyme

in the cases described above. Therefore, all six patients could have been in a state of physiologically elevated opioid levels when ACE inhibitor therapy was initiated. ACE inhibitors, in turn, have been shown to enhance opioid activity. Biological studies have shown that ACE inhibitors inhibit the peptidase responsible for hydrolysis of the endogenous opioid enkephalin [4], thus raising its level. Exercise is another physiologic state in which levels of endogenous opioids are increased (beta-endorphin). A further increase in beta-endorphin levels was noted in healthy volunteers when captopril treatment was added to an exercise test [5]. Naloxone terminated captopril-induced hallucinations in one of the cases cited above [2]. An additional case in which naloxone reversed hypotension caused by an overdose of captopril also points to amplification of the opioid system by the latter (reference available from authors).

Based on these data, we suggest that ACE inhibitors caused hallucinations by triggering a further increase in endogen-

ous opioid levels in patients in whom these levels were already physiologically elevated. Indeed, it is interesting that the intensity of the hallucinatory content in our patient lessened with the easing of the pain in her arm, despite the fact that she continued to take cilazapril. Cilazapril therapy was discontinued in our patient. During the subsequent 10 days the fly's visits dwindled and then ceased altogether.

The ages of the patients described here may suggest an increased vulnerability of the elderly to this adverse effect. Stress is often accepted as sufficient explanation for mental symptoms in the elderly. The above cases serve as a reminder that concomitant drug therapy should always be taken into account. Finally, on a reflective note, it is our impression that the clinical implications of ACE inhibitor-enhanced opioid activity deserve further attention.

References

1. Tarlow MM, Sakaris A, Scoyni R, Wolf-Klein G. Quinapril-associated acute psy-

chosis in an older woman [Letter]. *J Am Geriatr Soc* 2000;48(11):1533.

2. Gillman MNA, Sandyk R. Reversal of captopril induced psychosis with naloxone. *Am J Psychiatry* 1985;142(2):270.
3. Fontana F, Bernardi P. Relationship between plasma natriuretic factor and opioid peptide levels in healthy subjects and in patients with acute congestive heart failure. *Eur Heart J* 1993;14(2):219-25.
4. Hiranuma T, Iwao K. Almost complete protection from (met5)-enkephalin-Arg6-Gly7-Leu8 (Met-enk-RGL) hydrolysis in membrane preparations by the combination of amastatin, captopril and phosphoramidon. *J Pharmacol Exp Ther* 1997;281(2):769-74.
5. Handa K, Sasaki J. Effects of captopril on opioid peptides during exercise and quality of life in normal subjects. *Am Heart J* 1991;122(5):1389-94.

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