

ACE-inhibitors and hallucinations

Introduction

Angiotensin-converting enzyme (ACE) inhibitors are widely used for the treatment of hypertension and heart failure. The SPC's of the ACE-inhibitors describe several neuropsychiatric ADRs like *sleep disorders, confusion, depression, dream disorders, behavioral alterations, mood swings, nervousness and somberness* [1-11]. However (visual) hallucinations are not mentioned.

Reports

On March 24, 2006 the database of the Netherlands Pharmacovigilance Centre Lareb contained 6 reports of visual hallucinations associated with the use of the ACE-inhibitors captopril, trandolapril, lisinopril, ramipril, enalapril and fosinopril (table 1). All patients recovered after cessation of the suspect drug.

Table 1. reports of hallucinations associated with the use of angiotensin-converting enzyme inhibitors

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A M, 83	captopril 3dd 12.5 mg not specified	ibuprofen, paracetamol, hydroquinine	visual hallucinations	3 days, patient recovered within 1 day after cessation
B M, 59	trandolapril od 0.5 mg primary hypertension	Insulin actrapid	hallucinations, insomnia, non- inflammatory joint swelling	3 days, patient recovered after cessation
C M, 79	lisinopril od 5 mg not specified	Insuline mixtard, albuterol, pilocarpine, temazepam, epinephrine with guanethidine, theophylline, triamterene with epitizide, potas- sium,dipyridamole	visual hallucinations (ants walking against a dark background), dizziness	18 days, patient recovered after cessation
D F, 93	lisinopril od 0.5 mg primary hypertension	omeprazole, chlorthalidone	visual hallucinations ("insects")	2 days, patient recovered within 4 days after cessation
E M, 60	ramipril od 2.5 mg primary hypertension	amitriptyline, hydrochloro- thiazide, metoprolol	visual hallucinations (lights, saw wife that wasn't present), confusion	1 day, patient recovered after cessation
F F, 76	enalapril td 20 mg primary hypertension	chlordiazepoxide, glimiperide, lactitol	visual hallucinations (blurred people and strange men)	3 days after increase of the dose, patient recovered within 2 days after cessation

Other sources of information

SPCs

The SPC's of the ACE-inhibitors describe effects on mood, behavior and sleep [2]. Also behavioral alterations [3] and mood swings [5] are mentioned.

Literature

There are several case reports that describe patients who suffered from visual hallucinations induced by ACE-inhibitors.

Haffner *et al.* describe two cases of hallucinations in elderly patients. A 64-year-old man developed visual hallucinations as well as nightmares within 1 month after initiation of captopril 12.5 mg 3 times daily for congestive heart failure. His only other medication was furosemide 40 mg.

Visual hallucinations also occurred in a 73-year-old male after the start of enalapril, 5 mg 2 times daily, and resolved upon withdrawal of the therapy. One month later, captopril 12.5 mg 3 times daily elicited identical symptoms within 24 hours. Again, symptoms resolved after all ACE-inhibitor therapy was stopped. The patient had no preceding psychiatric disorder and did not drink alcohol regularly [12].

Rabinowitz & Reis report a case of a 70-year-old woman who had visual hallucinations, which manifested itself as insects in her soup, within 2 days after starting cilazapril 2.5 mg daily. Her other medication included paracetamol and dipyron to treat the pain of a fracture in her right arm, that had occurred one week earlier. She also used omeprazole, which she had been taking for 5 years. Two weeks later, the patient reported that she perceived a visual hallucination like seeing a fly roaming the periphery of her vision. Cilazapril was discontinued and the visual hallucinations resolved over the next 10 days [13].

Walker describes the case of a 92-year-old woman who suffered from vivid visual hallucinations 10 days after start of treatment with quinapril for hypertension. The patient had a past history of cataract surgery, left retinal vein hemorrhage and senile macular degeneration with severe visual impairment. After quinapril was discontinued her hallucinations stopped within one week, however her blood pressure had raised again [14].

Databases

On 24 March the Lareb database contained 6 reports on an ACE-inhibitors concerning hallucinations (ROR = 1.3; 95%CI 0.6 – 2.9).

On March 24 2006 the database of the Uppsala monitoring centre contains 97,293 reports on ACE-inhibitors. Among these reports are 218 reports of hallucinations. The association is not disproportionally present in the WHO nor the Lareb database.

Mechanism

ACE-inhibitors inhibit enkephalinase, this is the peptidase responsible for the hydrolysis of enkephalins, endogenous opioids which have potent effects on behavior. By inhibition of this enzyme the level of opioids is raised [13,15].

This is further illustrated by a case of confusion and hallucinations in a 76-year-old man who was given captopril 37.5 mg for severe congestive heart failure.

Reduction in dose did not help but in an experimental setting and after informed consent, intravenous naloxone (an opioid-antagonist) completely restored mental functioning [16].

In the article by Rabinowitz and Reis it was suggested that in some cases the level of endogenous opioids may have been already physiologically elevated in response to an underlying condition such as pain [13].

Conclusion

Lareb received 6 reports of visual hallucinations in association with ACE-inhibitors. In all of the reported cases a positive dechallenge is described which is supportive for a causal relationship. Though the association lacks disproportionality in the databases, the absolute number of reports in our database, together with a possible pharmacological explanation and several case-reports in the literature, support a causal relationship.

References

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