

ACE-inhibitors and hallucinations - an update

Introduction

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[®]), captopril, enalapril (Renitec[®]), fosinopril, lisinopril (Zestril[®]), perindopril (Coversyl[®]), quinapril (Acupril[®]), ramipril (Tritace[®]), and zofenopril (Zofil[®]) [1-9]. Most ACE-inhibitors are also registered in combination with other antihypertensive drugs.

Hallucinations are the perception of an external sensory stimulus where none exists. These can be somatosensory, visual, auditory, and olfactory.

Visual hallucinations are a clinical manifestation of neuroophthalmologic dysfunction resulting from a wide variety of underlying causes, such as epilepsy, migraine, and neurodegenerative disease. But also several drugs can cause visual hallucinations. Auditory hallucinations can arise from injury to any portion of the peripheral and central auditory pathways. Auditory hallucinations are most strongly linked to schizophrenia, but are also described in patients with Alzheimer disease and epilepsy. Several drugs are associated with auditory hallucinations [10].

In May 2006 Lareb described the association between hallucinations and the use of ACE-inhibitors in a quarterly report [11]. The current observation is an update of this association.

Reports

Between January 26th 1996 and June 12th 2014, the Netherlands Pharmacovigilance Centre Lareb received 15 reports of hallucinations associated with the use of ACE-inhibitors. No reports of hallucinations associated with the use of ACE-inhibitors combined with other antihypertensive drugs were received. Hallucinations reported were visual hallucinations (n=10), auditory hallucinations (n=3) and hallucinations NOS (n=3). One patient reported auditory as well as visual hallucinations.

The following ACE-inhibitors were reported: enalapril (n=5), perindopril (n=5), lisinopril (n=2), captopril (n=1), ramipril (n=1) andtrandolapril (n=1).

Most reports were reported by general practitioners (n=9). The other reports were received from pharmacists (n=3), consumers (n=2) and one report from a psychiatrist. Eight reports concerned women and seven reports concerned men. The median age was 69 years and ranged from 43 to 93 years. Time to onset varied from one day to ten months (median latency five days). Nine patients recovered after stopping treatment with the ACE-inhibitor. One patient reduced the dose and was recovering at the time of notification. One patient reported a positive rechallenge. In 13 reports the ACE-inhibitor was reported as the only suspect drug and no other drugs or causes were reported. In three reports metoprolol, atenolol or pregabalin were reported as co-suspect drugs. These drugs are also known to cause hallucinations [12-14]. However, in the report with metoprolol as co-suspect drug the patient had used metoprolol for two years without any problems and one month after start of enalapril the hallucinations started. Upon withdrawal of enalapril the hallucinations disappeared while metoprolol was being continued. In the report with atenolol start- and stopdates, action with drug and outcome were not provided. And in the report with pregabalin, the latency was six months after start of perindopril and a few weeks after start of pregabalin. However, whether these drugs were withdrawn or not was not reported, while the patient was

recovering. One patient reports hallucinations when using enalapril, however when switching to lisinopril the hallucinations disappeared.

A few reports will be described in detail:

A report from a general practitioner concerns a 73-year-old female with auditory hallucinations following administration of enalapril for hypertension with a latency of one day after dose change from 10 mg once a day to 20 mg once a day. The patient is recovering after changing the dose back to 10 mg once a day. This patient experienced the same adverse reaction two years earlier when changing the dose from 10 mg to 20 mg once a day.

Another report from a general practitioner concerns a 93-year-old woman with visual hallucinations, which occurred two days after starting lisinopril 5 mg daily for hypertension. As comedication she used omeprazol 20 mg daily and chlortalidone 12,5 mg daily. This patient was treated with risperidone and lisinopril was discontinued, whereafter the symptoms resolved.

Finally a report from a general practitioner concerns a 81-year-old female with visual hallucinations following administration of enalapril for hypertension with a latency of six days after start. The patient recovered after cessation of enalapril. Concomitant medications were indapamide, metformin, carbasalate calcium and omeprazole.

Other sources of information

SmPC

The SmPC's of the ACE-inhibitors describe several neuropsychiatric ADRs like *sleep disorders, confusion, depression, dream disorders, behavioural alterations, mood swings, nervousness and somberness*. However hallucinations are not mentioned, except in the SmPC of lisinopril [1-9].

Literature

Lareb previously described six of the 15 cases reported in this quarterly report in the Dutch Drug Bulletin (Geneesmiddelenbulletin) [15].

Furthermore, there are several other case reports that describe hallucinations induced by ACE-inhibitors. Nightmares and disturbed visual perceptions were reported within one month after initiation of captopril 12.5 mg three times daily for congestive heart failure in a 64-year-old male. His only other medication was furosemide 40 mg. Visual hallucinations also occurred in a 73-year-old male after beginning enalapril 5 mg two times daily, and resolved upon withdrawal of the therapy. One month later, captopril 12.5 mg three 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 [16].

Quinapril-induced confusion, disorientation and anxiety associated with visual hallucinations have been reported in isolated case reports [17,18]

Abrupt onset of symptoms within two hours after the first dose of 2.5 mg occurred in a 93-year-old woman who had been admitted two weeks earlier. She had been completely oriented prior to quinapril. Symptoms continued for five days until quinapril was discontinued, with rapid resolution of symptoms over the next 24 to 72 hours [17].

Within two days after beginning cilazapril 2.5 mg daily, a 70-year-old woman reported visual hallucinations manifesting as insects swarming in her soup, ascending her spoon and into her mouth. 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 five 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 ten days [19]. Visual hallucinations are also reported in a 51-year-old male who apparently took 27 lisinopril 10 mg tablets over a period of three or fewer days. The man also had multiorgan dysfunction. The abnormalities resolved after he was treated for acidosis and hyperkalemia and received hemodialysis to remove the lisinopril [20].

Databases

Table 1. Reports of hallucinations associated with the use of ACE-inhibitors in the Lareb, WHO and Eudravigilance database [21,22].

Database	Drug	Number of reports	ROR (95% CI)
Lareb	ACE-inhibitors	15	0.7 (0.4-1.2)
WHO	ACE-inhibitors	371	0.4 (0.4-0.5)
Eudravigilance	ACE-inhibitors	149	0.5 (0.5 – 0.6)

Prescription data

Table 2. Number of patients using ACE-inhibitors in the Netherlands between 2009 and 2013 [23].

Drug	2009	2010	2011	2012	2013
benazepril	331	294	263	247	219
captopril	33,712	30,215	26,853	24,164	21,763
enalapril	293,740	299,180	301,710	306,840	307,160
fosinopril	60,707	59,679	58,958	60,845	59,058
lisinopril	176,770	190,600	201,650	214,820	229,600
perindopril	214,810	232,840	245,980	262,450	278,280
quinapril	36,608	34,583	32,380	30,430	28,589
ramipril	52,504	54,293	55,614	57,188	58,157
zofenopril	4,935	5,159	4,970	4,533	4,164

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 [19,24]. 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 [25].

In the article by Rabinowitz and Reis [19] 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.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 15 reports of hallucinations associated with the use of ACE-inhibitors. Nine positive dechallenges and one positive rechallenge were reported. ACE-inhibitors differ in lipophilicity with fosinopril and zofenopril being the most lipophilic and lisinopril, captopril and enalapril the least lipophilic [26]. In our reports this latter group is primarily mentioned. Therefore high lipophilicity resulting in more blood-brain-barrier passage would not explain this effect.

An increased level of endogenous opioids by ACE-inhibitors is possibly responsible for the hallucinations. However, ACE-inhibitors are given to patients with a poor circulation and probably lesser oxygenation of the brain which could also be responsible for the hallucinations.

The association of ACE-inhibitors and hallucinations is not supported by a statistically significant disproportionality in the database of Lareb nor the WHO or Eudravigilance. However, the absolute number of reports in the Lareb database (although low compared to the wide spread use of ACE-inhibitors), together with a plausible pharmacological mechanism and several case-reports in the literature support a causal relationship. Since our quarterly report in 2006 nine new cases have been reported to Lareb. Therefore, it is important to continue to give this association close attention.

- Further investigation of the information of the marketing authorization holders and other national centres is needed to strengthen the signal

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This signal has been raised on November 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbqmeb.nl