

Rivastigmine and nightmares and abnormal dreams

Introduction

Rivastigmine (Exelon®, Permente®) belongs to the class of cholinesterase inhibitors. Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurons. Rivastigmine interacts with its target enzymes, acetyl- and butyrylcholinesterase, by forming a covalently bound complex that temporarily inactivates the enzymes [1].

Rivastigmine has been granted marketing authorization in the Netherlands since May 1998. The drug is indicated for *symptomatic treatment of mild to moderately severe Alzheimer's dementia and mild to moderately severe dementia in patients with idiopathic Parkinson's disease* [1].

Donepezil and galantamine are other cholinesterase inhibitors available on the Dutch market for the treatment of mild to moderately severe Alzheimer's dementia [2].

Sleep can be divided in two different states: non-rapid eye movement (non-REM) and rapid eye movement (REM) sleep [3]. In non-REM sleep neuronal activity and excitability are low, whereas in REM sleep the brain shows an activated behavioral state. Therefore, it is supposed generally that dreaming mainly occurs during REM-sleep, though recent literature gives evidence that REM sleep can occur without dreaming and vice versa [4,5].

Alzheimer's dementia has been linked to the loss of cholinergic function in the brain. Patients with Alzheimer's dementia show decreased REM sleep in proportion to the extent of their dementia, causing sleep disturbances [6]. Some studies investigate the effect of cholinesterase inhibitors on sleep in patients with Alzheimer's dementia [7-10]. Treatment with cholinesterase inhibitors enhance REM-sleep, REM density and the duration of the first REM sleep, and also reduces REM latency in patients with Alzheimer's dementia [10,11].

Reports

On January 9th 2014, the database of the Netherlands Pharmacovigilance Centre Lareb contained 2 reports of nightmares and 1 report of abnormal dreams associated with the use of rivastigmine. The first report was received in January 2005 and the last report was received in June 2013.

Case A (48257)

This report from a geriatrician describes a male patient, aged 61-70 years old, suffering from nightmares, excessive sweating, restlessness during the night and nausea at intervals following administration of rivastigmine 2dd 6 mg for Alzheimer's disease with a latency of an unknown number of days after start. Concomitant medication were carbasalate calcium 1dd 100mg, metoprolol 1dd 100mg, rosuvastatin 1dd 20mg, and quinapril 1dd 2.5mg. Carbasalate calcium and metoprolol were started 5 years prior to the reaction. The startdate of rosuvastatin and quinapril is unknown. At the lower dose of 2dd 4.5mg, nightmares occurred occasionally. After the withdrawal of rivastigmine, the patient fully recovered.

Case B (66587)

This report from a pharmacist concerns a male patient, aged 61-70 years, with nightmares following administration of gabapentin for pain and rivastigmine for Parkinson's dementia. The reaction occurred after the start of gabapentine 1dd 300mg and a simultaneous dose increase of rivastigmine to a dose of 2dd 6mg. Rivastigmine was started 6 weeks earlier. Concomitant medications were levothyroxine 1dd 0.125mg, tamsulosine 1dd 0.4mg, ropinirol 1dd 2mg, carbasalate calcium 1dd 100mg, levodopa/benserazide 1dd 100/25mg and isosorbide mononitrate 1dd 25mg. All concomitant drugs were started 3 to 6 years prior to the reaction. The reaction improved after the dose for rivastigmine was decreased to 2dd 4.5mg. According to medication history of the patient, the dose for gabapentin was also reduced, or the patient had poor drug compliance. The previously established dose 1dd 300mg for gabapentine was maintained.

Case C (155819)

This report from a geriatrician describes a male patient, aged 70 years and older, with bad dreams following administration of rivastigmine transdermal patch 9.5mg/24h for Alzheimer's disease with a latency of 12 days after start. The patient recovered 11 days after the drug rivastigmine was withdrawn. Concomitant medications were valsartan 1 dd80mg, paracetamol 4dd 1000mg, glimepiride 1dd 1mg, simvastatin 1dd 20mg, tamsulosin 1dd 0.4mg, acetylsalicylic acid 1dd 80mg and metformin 2dd 500mg.

Other sources of information

SmPC

Neither the Dutch SmPCs of rivastigmine, galantamine and donepezil nor the US SmPCs of rivastigmine (Exelon®) and galantamine (Razadyne®) describe abnormal dreams or nightmares as a possible ADR [1,12-17]. However, the US SmPC of donepezil (Aricept®) [18] mentions abnormal dreams as a side effect.

Literature

In spite of lacking literature on an association between rivastigmine and abnormal dreams or nightmares, several case-reports were published involving other cholinesterase inhibitors [7,19-21]. Cholinergic overactivity in the central nervous system can cause sleep disturbances, including abnormal dreams and nightmares [22].

Ross et al. [7] describe two cases of donepezil induced nightmares in patients with Alzheimer's disease. In both patients nightmares occurred immediately after the start of the treatment. Donepezil was given at bedtime. In both cases a positive de- and rechallenge was performed. When donepezil was administered in the morning, no sleep problems were reported.

Kitabayashi et al. [19] outline a case of a 79-year-old female patient with mild cognitive impairment (MCI) who experienced frequent nightmares following donepezil treatment with a latency of a few days after start. A positive dechallenge was performed. Two years later donepezil was re-administered after the diagnosis of Alzheimer's disease. This time donepezil administration no longer caused nightmares. The authors suggest that cholinergic over-activation may cause more severe and frequent sleep problems in MCI, in which cholinergic dysfunction is less apparent than in Alzheimer's disease.

The case-report of Iraqi and Hughes [20] describes a 77-year-old male patient who was treated with galantamine for dementia. Three weeks after the start of the treatment, he suffered from nightmares. A positive de- and rechallenge was performed. At a later point in time, treatment with donepezil was initiated without any recurrence of nightmares over the next ten months.

In another case-report by Corbo et al. [21] a male patient, aged 90 years, with Alzheimer's disease was treated with galantamine. After the start of galantamine nightmares developed and temporally increased with dose titration. The patient recovered after discontinuation.

Singer et al. [23] demonstrate a clear-cut relationship between the occurrence of nightmares and the time of donepezil intake. The influence of time point of donepezil intake was investigated in patients with Alzheimer's dementia. Eight out of 103 patients suffered from nightmares during treatment with donepezil. They all took donepezil in the evening. After the time point of donepezil intake was changed from the evening to the morning, all eight patients recovered from nightmares. The authors stated that pharmacokinetic possibly plays an important role, since there is a small difference between the steady-state plasma concentration and the maximum plasma concentration after evening administration of donepezil [24]. It is suggested that the influence of time point of intake on the occurrence of nightmares also applies to rivastigmine and galantamine. The authors observed the same effect in three patients who were treated with galantamine.

Databases

Table 1. Total reports of abnormal dreams and nightmares associated with rivastigmine in the databases of Lareb, WHO and EMA on January 9th 2014.

Drug	Number of reports (nightmares/abnormal dreams)	Combined ROR (95% CI)
Rivastigmine	Lareb: 3 (2/1)	1.3 (0.4 – 4.0)
	WHO: 52 (34/18)	1.5 (1.2 – 2.0)
	Eudravigilance: 47 (34/13)	1.4 (1.1 – 1.9)

Prescription data

Table 2. Total number of patients using rivastigmine in the Netherlands between 2008 and 2012 [25].

	2008	2009	2010	2011	2012
Rivastigmine	11,272	13,634	15,007	15,625	16,154

Mechanism

Assuming that dreaming is, to a great extent, associated with REM-sleep, it seems plausible that alteration of brain activity during this sleep period can provoke abnormal dreams and nightmares. Cholinesterase inhibitors, like rivastigmine, can increase the activation of the visual association cortex by their influence on cholinergic afferent nerves during REM-sleep [10,11,23]. This effect on REM-sleep seems to occur only at higher doses of cholinesterase inhibitors [9,26], indicating a dose-depending effect.

Class effect

The Lareb database contains only one report of nightmares in association with another cholinesterase inhibitor. This report describes a male patient, aged 73 years old, suffering from nightmares and hyperhidrosis 1 week after dose increase of galantamine from 2dd 8mg to 1dd 24mg. The patient recovered after the withdrawal of galantamine. Despite the small number of other reports, the postulated mechanism suggests a class effect.

Discussion and conclusion

Lareb received two reports of nightmares and one report of abnormal dreams associated with the use of rivastigmine in patients with Alzheimer's or Parkinson's dementia. Two patients recovered after withdrawal of rivastigmine. One patient recovered after dose reduction, suggesting a dose-dependent ADR. Despite of an existing relationship between REM sleep behaviour disorders and neurodegenerative diseases like Parkinson's disease and Lewy Body dementia [27], the strong temporal relationship between the onset of nightmares or abnormal dreams and the start of rivastigmine in the Lareb reports indicates a causal relationship. The WHO database showed significant disproportionality of abnormal dreams and nightmares associated with the use of rivastigmine.

Rivastigmine is thought to cause abnormal dreams and nightmares by increased activation of the visual association cortex, due to the influence on cholinergic afferent nerves during REM-sleep [10,11,23]. In literature, several case-reports were published involving other cholinesterase inhibitors [7,19-21].

The occurrence of abnormal dreams and nightmares is a new signal associated with the use of rivastigmine. Further investigation of the marketing authorization holders is advisable.

- Further investigation 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 May 2014. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgbmeb.nl/cbgb/en/default.htm or the responsible marketing authorization holder(s).