HMG-CoA-reductase inhibitors and nightmares or abnormal dreaming

Introduction

HMG-CoA-reductase inhibitors are widely used in primary and secondary prevention of cardiovascular diseases because of their effects on both the total cholesterol level and the LDL-cholesterol level. HMG-CoA-reductase inhibitors are competitive inhibitors of 3-hydroxy-3-methylglutargyl coenzyme-A reductase, which plays a role in the synthesis of cholesterol. The adverse drug reactions most frequently associated with the use of HMG-CoA-reductase inhibitors are gastrointestinal complaints, myalgia and slight elevation of the liver-enzymes. More rarely, severe adverse drug reactions like myopathy and rhabdomyolysis may occur [1].

A nightmare is defined by the DSM IV criteria as a frightening dream. Clinically the most common definition for nightmare is an unpleasant or frightening dream usually occurring in REM sleep (American Academy of Sleep Medicine) [2]. Suppression of REM sleep can result in an increased intensity of the REM episodes, which can be manifested as nightmares [3].

Nightmares or abnormal dreams are not mentioned in the SmPC of HMG-CoA-reductase inhibitors currently marketed in the Netherlands (simvastatin, atorvastatin, fluvastatin, pravastatin and rosuvastatin) [4-8]. The SmPC of fluvastatin and atorvastatin mention insomnia, the SmPC of pravastatin describes insomnia as well as sleep disturbances.

Reports

Until March 4, 2008 the Netherlands Pharmacovigilance Centre Lareb received 18 reports of nightmares (Table 1) and nine reports of abnormal dreaming (Table 2) associated with the use of HMG-CoA-reductase inhibitors.

Of the 18 reports of nightmares, only one report originated from a consumer (patient R), the majority or reports came from general practitioners. 11 patients recovered after withdrawal of the suspected drug. In five of these patients re-introduction of the suspected drug took place, resulting in a recurrence of symptoms (positive rechallenge). Both patient D and J finally switched from simvastatin to atorvastatin without complaints.
In another patient (R) simvastatin was not discontinued, but the dose was reduced, after which symptoms diminished; dose increase resulted in worsening of symptoms. Finally simvastatin was discontinued.
Reports E, F, and G concern the same patient, a male of 73 years old, who experienced nightmares, agitation and diarrhea on simvastatin, cerivastatin and atorvastatin respectively. After he discontinued atorvastatin, he never experienced nightmares anymore.
Of the 18 reports of nightmares, in eight cases a beta-blocker was used as concomitant medication, of which six times metoprolol was used. beta-blocking agents have been associated with nightmares previously [3].

Table 1. Reports of nightmares associated with the use of HMG-CoA-reductase inhibitors.

Patient, Number, Sex, age	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset Action with drug Outcome
A 13716 M, 54	simvastatin 10 mg hypercholesterolaemia	metoprolol	nightmares	45 days unknown unknown
B 15907 F, 63	simvastatin 10 mg	metoprolol amlodipine	nightmares agitation headache	7 months unknown unknown
C 22031 M, 58	pravastatin 10 mg hypercholesterolaemia	isosorbide dinitrate acetylsalicylic acid diltiazem	nightmares	4 months unknown unknown
D 32380 F, 57	simvastatin 20 mg hypercholesterolaemia	omeprazole losartan sotalol	nightmares	11 weeks discontinuation recovered rechallenge pos.
E 34505 M, 73	simvastatin 10 mg unknown	acetylsalicylic acid quinapril	nightmares agitation diarrheoa	unknown discontinued unknown
F 34506 M, 73	cerivastatin 0.1 mg unknown	acetylsalicylic acid quinapril	nightmares agitation diarrhoea	unknown discontinued unknown
G 34507 M, 73	atorvastatin (unknown dose) unknown	acetylsalicylic acid quinapril	nightmares agitation diarrhoea	unknown discontinued recovered
H 37477 M, 54	simvastatin 10 mg hypercholesterolaemia	fosinopril amlodipine carvedilol doxazosine	nightmares	days discontinued recovered
I 41924 F, 59	simvastatin 20 mg hypercholesterolaemia	esomeprazole	nightmares myalgia	8 hours discontinued unknown
J 42720 M, 75	simvastatin 20 mg unknown	acetylsalicylic acid	nightmares anxiety	unknown discontinued recovered
K 51368 M, 70	simvastatin 20 mg coronary artery disease	metoprolol clopidogrel losartan	nightmares	unknown discontinued recovered rechallenge pos.
L 53671 M, 70	simvastatin 20 mg hypercholesterolaemia	metformin glibenclamide	nightmares	4 days discontinuation recovered
M 59684 M, 61	atorvastatin 10 mg hypercholesterolaemia	sulfasalazine lisinopril	nightmares	unknown discontinued recovered rechallenge pos.

Patient, Number, Sex, age	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset Action with drug Outcome
N 60880 M, 65	simvastatin 20 mg prevention	tolbutamide metformin	nightmares	40 days discontinued recovered
O 62619 M, 60	simvastatin 40 mg cardiovascular risk	metoprolol	nightmares	5 months discontinued recovered rechallenge pos.
P 70165 F, 60	atorvastatin 20 mg unknown	amitriptyline pantoprazole metoprolol	nightmares somnambulism	6 years discontinued recovered
Q 71313 F, 58	simvastatin 40 mg hypercholesterolaemia	hydrocholorothiazide metoprolol	nightmares	hours discontinued recovered rechallenge pos.
R 74267 M, 55	simvastatin 40 mg hypercholesterolaemia	not reported	nightmares myalgia malaise	10 days dose reduction-> symptoms improved dose increase-> worsening final discontinuation-> recovered with sequel

Of the nine reports of abnormal dreaming, two were reported by consumers (F and I), the other reports were done by general practitioners and pharmacists.
five patients recovered after withdrawal of the suspected drug. In two of these patients (E,H) re-introduction of the suspected drug took place, resulting in a recurrence of symptoms, in patient H however the symptoms were not as severe as on previous administration. In patient D, beside simvastatin, also nifedipine and pindolol were suspected as causative drug for the development for abnormal dreams. The reaction however developed after dose increase of simvastatin, the dose of the other drugs was not altered.
For reports of abnormal dreaming, in four of the nine reports a beta-blocker was involved.

Table 2. Reports of abnormal dreams associated with the use of HMG-CoA-reductase inhibitors.

Patient, Number, Sex, age	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset Action with drug Outcome
A 8081 F, 75	simvastatin 10 mg lipoprotein A	acetylsalicylic acid bisoprolol	dreaming abnormal	4 months discontinued recovered
B 18404 M, 61	pravastatin 20 mg bid unknown	budesonide salmeterol carbasalate calcium	dreaming abnormal visual hallucination	weeks after dose-increase to bid discontinued recovered
C 18623	simvastatin 20 mg	perphenazine	dreaming abnormal	9 months

Patient, Number, Sex, age	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset Action with drug Outcome
F, 68		diazepam diclofenac artificial tears betahistine acetylsalicylic acid orphenadrine		unknown unknown
D 19674 M, 46	simvastatin 40 mg unknown also suspected: nifedipine 30 mg unknown pindolol 20 mg unknown	carbasalate-calcium	dream delirium	3 months after dose increase dose decreased unknown years continued unknown years continued unknown
E 26040 F, 71	simvastatin 20 mg hypercholesterolaemia	sotalol	dreaming abnormal	unknown discontinued recovered rechallenge pos.
F 43900 M, 68	rosuvastatin 10 mg unknown	not reported	dreaming abnormal	3 weeks continued not recovered
G 60832 F, 71	simvastatin 20 mg hypercholesterolaemia	oxazepam, dipyridamole acetylsalicylic acid pantoprazole valsartan amlodipine sertraline	excessive dreaming confusion	1 day discontinued (after months) recovered
H 71309 F, 72	rosuvastatin 10 mg hypercholesterolaemia	metoprolol losartan carbasalate – calcium	dreaming abnormal	1 day discontinued recovered rechallenge pos.
I 74706 F, 58	simvastatin 40 mg hypercholesterolaemia	sotalol lisinopril/ hydrochlorothiazide	dreaming abnormal insomnia	2 days dose reduction not yet recovered

Other sources of information

Literature

Gregoor described the occurrence of nightmares in a 72-year-old woman following atorvastatin therapy. The patient, who had a history of hypertension, hypothyroidism, heart failure, and chronic renal failure, was initiated on atorvastatin 10 mg once daily for hypercholesterolemia. Concurrent medications included

levothyroxine 75 micrograms/day, amlodipine 5 mg/day, atenolol 100 mg/day, and losartan 50 mg/day. Five days into the atorvastatin treatment, the patient experienced extreme nightmares every night for two and a half weeks. Subsequently, atorvastatin was discontinued for five days which put an end to the nightmares. A rechallenge with atorvastatin caused the nightmares to recur and, upon discontinuation of atorvastatin, to disappear [9].

Boriani et al. described nightmares and sleep disturbances in a 55-year-old man, while he was treated with simvastatin 10 mg/day and metoprolol 100 mg twice daily for coronary artery disease, hypertension, and hypercholesterolemia. His other medications included aspirin 325 mg/day and nifedipine 60 mg/day. Three months after initiation of therapy, the patient complained of restless nights and nightmares. Metoprolol was reduced to 50 mg/day, with no improvement in his sleep problems. Two weeks later, simvastatin was discontinued and pravastatin 20 mg/day was substituted. His quality of sleep improved, although he still had nightmares. Atenolol 100 mg/day was substituted for metoprolol. Thereafter, the patient ceased to have nightmares and he had no problems with sleep over six months of follow-up. Sleep disturbance recurred after a later attempt to reintroduce simvastatin in place of pravastatin. The same effect occurred when, during treatment with pravastatin, substitution of atenolol with metoprolol was attempted. In this case the statins may have interacted with metoprolol, and it may have been relevant that metoprolol is more lipid-soluble than atenolol [10].
No publications were found on nightmares or abnormal dreaming associated with the HMG-CoA-reductase inhibitors fluvastatin, pravastatin en rosuvastatin.

Databases

On March 4, 2008 the Lareb database contained 18 reports of nightmares associated with HMG-CoA-reductase inhibitors, which, as a group, was not disproportional (ROR 1.0, 95% CI 0.6-1.6). The 13 cases of nightmares occurring in relation to the use of simvastatin however were disproportionally represented (ROR 1.9, 95% CI 1.0-3.3).
The nine reports of abnormal dreaming on HMG-CoA-reductase inhibitors, as a group or individually, were not disproportionally reported.

On March 4, 2008 the WHO Collaborating Centre database contained several reports on nightmares (paroniria) associated with the individual HMG-CoA-reductase inhibitors; these reports were disproportionally represented for simvastatin, pravastatin, rosuvastatin and fluvastatin, but not for atorvastatin (Table 3).

Table 3. WHO database: Reporting odds ratio for nightmares (paroniria) in association with HMG-CoA-reductase inhibitors.

Drug	Number of reports	ROR (95% CI)
simvastatin	154	2.5 (2.1 - 2.9)
pravastatin	54	2.3 (1.7 - 3.1)
rosuvastatin	24	1.7 (1.1 - 2.6)
fluvastatin	24	2.7 (1.8 - 4.1)

Drug	Number of reports	ROR (95% CI)
atorvastatin	68	1.3 (0.98 - 1.6)

The WHO database contained reports of abnormal dreaming in association with all individual HMG-CoA-reductase inhibitors; with the exception of rosuvastatin, none of these associations reached statistical significance (Table 4).

Table 4. WHO database: Reporting odds ratio for dreaming abnormal in association with HMG-CoA-reductase inhibitors.

Drug	Number of reports	ROR (95% CI)
simvastatin	50	1.3 (0.96 - 1.7)
pravastatin	15	1.0 (0.61 - 1.7)
rosuvastatin	20	19.5 (12.5 - 30.5)
fluvastatin	7	1.7 (0.83 - 3.7)
atorvastatin	42	1.2 (0.91 - 1.7)

On June 8, 2008, the Eudravigilance database contained 37 reports of the five statins, marketed in the Netherlands associated with nightmares as serious reaction: 16 females and 21 males between 46 and 98 years were affected. Most reactions were reported serious due non-specified reasons (n=23), in six cases the disabling character of the nightmares was reason to classify the reaction as serious. In thirteen cases due to extensive somatic medical history or reported psychiatric co-morbidity alternative conditions like delirium or psychosis could not be ruled out. Hallucinations were reported explicitly in three reports.

Mechanism

Agargun performed a study in which a relation between nightmares and serum lipid levels was examined. Fifteen subjects who met DSM-IV criteria for the diagnosis of nightmare disorder and 15 healthy control subjects participated in the study. Patients with nightmares had lower serum triglyceride, lower total cholesterol, and lower LDL levels than healthy control subjects. The authors suggest an association between nightmares and low serum lipid levels. The exact mechanism of this association is not clear. Various neurotransmitters (serotonin, histamine, GABA, acetylcholine) and hormones participate in sleep regulation. The production of REM sleep depends on the decrease of serotonergic tone in brain stem structures. Membrane cholesterol modulates the functional properties of the 5-HT transporter by specific molecular interactions. Low cholesterol may be related to serotonergic inhibition in the brain during nightmares [11].

Fuchs reacted on the publication of Gregoor upon atorvastatin. He postulated that the nightmares might not be a direct effect of atorvastatin. Statins exert a significant inhibition of tryptophan-degrading enzyme indeleamine(2.3)-dioxygenase. Tryptophan is a precursor of serotonin, and limitation of tryptohphan availability negatively affects serotonin production [12].

In a literature review examining drug- induced nightmares it has been suggested that dopamine stimulation may be causally associated with nightmares [3].

Lowering of plasma cholesterol has been associated with increased dopamine levels in one prospective study [13].

Discussion

Lareb received 18 reports of nightmare and nine reports of abnormal dreaming. Of the 18 reports of nightmares, in eight cases a beta-blocker was used as concomitant medication, of which six times metoprolol was involved. For reports of abnormal dreaming, in four of the nine reports a beta-blocker was involved. Beta-blockers are known for causing sleep disturbances and nightmares. In all received cases however the beta-blocker was used as chronic treatment.
Other concomitantly taken drugs, including ACE inhibitors, have been related to nightmares as well. Also these drugs were taken as chronic treatment.
The nightmares might not have been a direct effect of HMG-CoA-reductase inhibitors, but may perhaps have developed by an influence of these statins on the used concomitant medications. No information upon relevant interactions between HMG-CoA-reductase inhibitors and concomitantly taken drugs (beta-blockers, ACE inhibitors, AII antagonists) however could be found; with calcium antagonists, a small risk of increase in plasma level of CYP3A4 mediated HMG-CoA-reductase inhibitors could be observed [1,14].
The majority of reported nightmares and abnormal dreaming were associated with simvastatin, the most prescribes statin in the Netherlands. Only two publications on nightmares are available, one associated with simvastatin, the other with atorvastatin. No publications are available upon comparative effects of individual HMG-CoA-reductase inhibitors and nightmares, with respect to differences in lipophilicity. However, several studies have been performed for comparison of lipophilic (simvastatin, lovastatin) and hydrophilic (pravastatin, fluvastatin) statins on sleep. Some studies showed less sleep disturbances with hydrophilic drugs, because they cross the blood-brain barrier to a lesser extent [15]. Contradictory to this, other more recent studies, found no differences on sleep between lipophilic and hydrophilic HMG-CoA-reductase inhibitors [16,17]. Furthermore the reports of nightmares in the database of the WHO show comparable odds ratios for lipophilic as well as hydrophilic HMG-CoA-reductase inhibitors.

Conclusion

The Netherlands Pharmacovigilance Centre Lareb received 18 reports of nightmares and 9 reports of abnormal dreams with the use of HMG-CoA-reductase inhibitors. Nightmares or abnormal dreams are not mentioned in the SmPCs of HMG-CoA-reductase inhibitors currently marketed in the Netherlands (simvastatin, atorvastatin, fluvastatin, pravastatin and rosuvastatin). Although a role of confounding factors like concomitant medication can not be excluded, the number of reports with clearance of symptoms after withdrawal of the statin and recurrence of nightmares after re-introduction is high. These data are confirmed by the reports on nightmares in association with of HMG-CoA-reductase inhibitors in the WHO database. A few reports of nightmares on statins are described in the literature, with a possible mechanism related to the serotonergic/dopaminergic system. It should be considered to mention nightmares in the SmPCs of the HMG-CoA-reductase inhibitors.

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