Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

HMG-CoA-reductase inhibitors and neuropathy: reports to the Netherlands Pharmacovigilance Centre

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ABSTRACT

The number of patients taking HMG-CoA-reductase inhibitors for hypercholesterolaemia is growing rapidly. Treatment with HMG-CoA-reductase inhibitors significantly reduces the risk of cardiovascular morbidity and mortality, but may rarely cause serious adverse drug reactions (ADRs). The most serious ADRs of HMG-CoA-reductase inhibitors are musculoskeletal symptoms including myopathy and myositis, (life-threatening) rhabdomyolysis and liver failure. Furthermore, peripheral neuropathy might also occur, especially after long-term use of HMG-CoA-reductase inhibitors. Because of the severity and the relative rarity of HMG-CoA-reductase-induced neuropathy, the Netherlands Pharmacovigilance Centre Lareb has analysed its database of reported ADRs for reports concerning neuropathy associated with the use of HMG-CoA-reductase inhibitors. Until June 2005, Lareb received 17 reports of neuropathy, peripheral neuropathy and polyneuropathy and in addition two reports of aggravation of existing polyneuropathy associated with the use of HMG-CoA-reductase inhibitors. The associations neuropathy, peripheral neuropathy and polyneuropathy and the use of HMG-CoA-reductase inhibitors are statistically significantly more often reported to Lareb. The average time to onset supports conclusions of previous studies and case reports that especially long-term exposure increases the risk for peripheral neuropathy. Considering the increasing number of patients taking HMG-CoA-reductase inhibitors, health care professionals should be aware of the possible role of these drugs in neuropathy.

KEYWORDS

HMG-CoA-reductase inhibitor, hypercholesterolaemia, neuropathy

INTRODUCTION

A rapidly growing number of patients are taking hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA)-reductase inhibitors to reduce cholesterol levels in the framework of the primary and secondary prevention of atherosclerosis. Furthermore, HMG-CoA-reductase inhibitors reduce the risk of stroke and peripheral vascular disorders.[1] The Heart Protection Study showed a significant reduction in the risk of cardiovascular morbidity and mortality after treatment with HMG-CoA-reductase inhibitors. Death due to any vascular cause was reduced by 17% ($p<0.0001$).[2]
Besides their efficacy, HMG-CoA-reductase inhibitors can also produce a variety of adverse drug reactions (ADRs). However, clinically significant ADRs are rare and discontinuation due to ADRs varies from only 1.0 to 4.8%.[1] The most serious ADRs are musculoskeletal symptoms including myopathy and myositis, (life-threatening) rhabdomyolysis,[3,4] and liver failure.[1] Elevation of transaminase levels may occur in 1 to 3% of the patients taking HMG-CoA-reductase inhibitors.[5] Post-marketing studies and case reports suggest that HMG-CoA-reductase inhibitors are also associated with peripheral neuropathy,[6-10] for which the risk significantly increases after long-term use.[6]

Peripheral neuropathy

Peripheral neuropathy is a common term used to define disorders of the peripheral nervous system. The clinical symptoms of peripheral neuropathy may vary widely and include symptoms as paraesthesia or hyperaesthesia of the extremities, sensory loss, muscle weakness, atrophy and autonomic symptoms.[11,12] Electrodiagnostic investigations, including nerve conduction studies and needle electromyography, may be necessary for accurate diagnosis of peripheral neuropathy.[12]

Drug-induced neuropathy is in general characterised by degeneration of the axonal nerve.[8,13] However chronic axonal polyneuropathy has many other possible causes, such as diabetes mellitus, nutritional deficiencies, chronic renal failure, malignancies, and alcohol abuse.[12]

Frequency

Drug-induced neuropathy does not occur often. Several drugs are associated with neuropathy, for example chemotherapeutics, antibiotics, cardiovascular drugs such as amiodarone, enalapril, hydralazine and the HMG-CoA-reductase inhibitors.[1] The overall prevalence of peripheral neuropathy is approximately 2400 per 100,000 population (2.4%), but in patients older than 55 years the prevalence rises to about 8000 per 100,000.[12] Possible risk factors for developing peripheral neuropathy are hyperlipidaemia,[14] diabetes mellitus and the use of alcohol,[11] with diabetes mellitus being the most important risk factor. The incidence of peripheral neuropathy not associated with alcohol or diabetes is 1.5 per 10,000 person-years.[11,15] The incidence of peripheral neuropathy caused by the use of various drugs is not known. However, epidemiological results suggest that the incidence of peripheral neuropathy associated with the use of HMG-CoA-reductase inhibitors is 1 in 14,000 person-years.[1]

Drug-induced peripheral neuropathy in general occurs shortly after the first exposure to drugs or after a change in medication. However, experiences with HMG-CoA-reductase inhibitors show that neuropathy can also occur many months or years after starting the drug.[13] More important, the risk for neuropathy significantly increases after long-term use of HMG-CoA-reductase inhibitors.

METHODS

The Netherlands Pharmacovigilance Centre Lareb collects and analyses reports of ADRs of marketed drugs provided by health professionals on a voluntary basis on behalf of the Dutch Medicines Evaluation Board. After being received by Lareb, reports are assessed and personalised feedback is provided to the reporter. The reported suspected ADRs are coded using the MedDRA terminology.

The relationship between HMG-CoA-reductase inhibitors and reports concerning neuropathy were evaluated mathematically by computing the reporting odds ratios (ROR). The ROR compares the frequency of the reported ADR for a certain drug with the frequency of reports of that adverse drug reaction for all other drugs in the database. A statistically significant ROR may be indicative of a higher risk for that particular event during the use of a specific medication, but is never conclusive for the actual existence of a causal relation. Additional pharmacoepidemiological studies are needed to determine the actual incidence of a possible ADR. The RORs and 95% confidence intervals (95% CI) were calculated in a case/noncase design.[16] Reports received until 1 June 2005 for which age and gender were reported were included in the analysis. Reports concerning the MedDRA terms neuropathy, peripheral neuropathy and polyneuropathy were considered as cases, all other reports as noncases. Index reports included all reports on an HMG-CoA-reductase inhibitor (ATC code beginning with C10AA); all other reports were controls. The unadjusted ROR and the ROR adjusted for age, gender and the use of antidiabetic medication (ATC code beginning with A10) were calculated by means of logistic regression analysis.[17,18] SPSS software package, version 14, was used for statistical calculations.

RESULTS

Reports in Lareb database

From 1984 to June 2005, Lareb received 17 reports of neuropathy and two reports of aggravation of polyneuropathy associated with the use of HMG-CoA-reductase inhibitors (*table 1*).

Of the 19 reports, nine reports concerned simvastatin, six atorvastatin, three pravastatin and one rosuvastatin. In 13 cases the suspect HMG-CoA-reductase inhibitor was discontinued and in seven of these cases the patient (partially) recovered. The latency period ranges from a few months until years with a mean time to onset of 23.4 months. The time to onset of *de novo* polyneuropathy can be up to 72 months with a mean time to onset of 23.4 months.

Strength of the association

In June 2005 the Lareb database contained 45,325 reports in which the patient's age and gender were known. Of these reports 1911 concerned the use of HMG-CoA-reductase inhibitors and in 18 of them the reported ADR was neuropathy, peripheral neuropathy or polyneuropathy. The characteristics of the HMG-CoA-reductase inhibitors dataset differ significantly from the characteristics of the rest of the dataset (*table 2*). After adjustment for the influence of gender, age and the concomitant use of antidiabetic medication, the ROR for neuropathy – including the MedDRA terms neuropathy, peripheral neuropathy and polyneuropathy and HMG-CoA-reductase inhibitors – was 3.7 (95% CI: 2.2 to 6.2), indicating that neuropathy is significantly more reported during treatment with statins as compared with any other drug class in the Lareb database.

Reports in WHO database

Reports of various pharmacovigilance centres worldwide are forwarded to the database of the World Health Organisation

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

A	Sex, age	Drug, dose if known	Concomitant medication	Suspected ADR	Time to onset, outcome	Remarks
B	M, 25	Simvastatin, 1 dd 10 mg	Not reported	Neuropathy, paraesthesia of arms and legs	8 months, recovered after withdrawal	
C	F, 59	Simvastatin, 1 dd 20 mg	Enalapril Labetalol	Myopathy, peripheral neuropathy	2 years, not recovered after withdrawal	
D	M, 56	Atorvastatin, 1 dd 20 mg	ASA	Peripheral neuropathy up to knees and hands	5 months, almost completely recovered after withdrawal	
E	M, 65	Pravastatin, 1 dd 10 mg	Lansoprazole Oxazepam ASA	Peripheral neuropathy	2 years, recovered after withdrawal	EMG: no indication for polyneuropathy
F	F, 69	Simvastatin, 1 dd 20 mg	Not reported	Neuropathy (cause unknown)	3 weeks, unknown	
G	M, 71	Pravastatin, 1 dd 40 mg	Lisinopril Budesonide ASA	Pain and burning lower right leg and foot (at night)	5 years, recovering after withdrawal	EMG: no abnormalities, possibly minor neuropathy peroneal nerve
H	M, 77	Simvastatin, 1 dd 40 mg; Sulphamethoxazole/ trimethoprim 2 dd 960 mg	Tamsulosin Omeprazole Amiodarone Amlodipine Furosemide Acenocoumarol Spironolactone Quinapril Prednisolone Triamterene Hydrochlorothiazide	Axonal polyneuropathy, hepatitis, myositis, renal failure	1 year, unknown	EMG: senso-motoric axonal polyneuropathy; patient suffers from progressive renal failure
I	M, 52	Simvastatin, 1 dd 10 mg	Phenytoin	Anoxal polyneuropathy	4 years, unknown	Patient suffers from epilepsy
J	M, 60	Atorvastatin	Dipyramidole Folic acid, enalapril Hydrochlorothiazide ASA	Peripheral neuropathy, cramps in extremities, muscle weakness of legs	6 years, not recovered yet one month after withdrawal	Patient suffers from vitamin B12 deficiency
K	M, 64	Pravastatin, 1 dd 40 mg	Amlodipine, losartan Sotalol ASA	Polyneuropathy	3 weeks, not recovered	
L	V, 63	Atorvastatin, 1 dd 10 mg	Allopurinol Diazepam Furosemide Metoprolol	Peripheral neuropathy, speech and walking difficulties	22 months, five months after withdrawal not yet recovered	EMG: no abnormalities
M	M, 75	Simvastatin, 1 dd 40 mg	ASA Acenocoumarol	Aggravation of existing polyneuropathy	1 day after starting, symptoms decreased after withdrawal	
N	M, 45	Rosuvastatin	Not reported	Polyneuropathy	2 weeks	
O	M, 66	Atorvastatin	Thyroxin Trichlormethiazide Metoprolol ASA	Polyneuropathy	4 years, recovered 1 month after withdrawal	
P	M, 74	Simvastatin	ASA	Aggravation of existing polyneuropathy, erectile dysfunction and decreased ejaculation	12 weeks after starting, not recovered after withdrawal	Medical history of non-progressive polyneuropathy
Q	F, ?	Atorvastatin	Not reported	Polyneuropathy, increased cholesterol levels	Time to onset and outcome unknown	Patient suffers from diabetes mellitus
R	M, 71	Atorvastatin	ASA Diltiazem Enalapril	Polyneuropathy	5.5 years, recovered after withdrawal	
S	M, 45	Simvastatin	Enalapril Hydrochlorothiazide ASA	Polyneuropathy	2 months, simvastatin withdrawn, patient not recovered yet	
T	M, 78	Simvastatin	ASA Metoprolol	Peripheral neuropathy	4.5 years, simvastatin withdrawn patient not recovered yet	Patient suffers from diabetes mellitus

M = male; f = female; ADR = adverse drug reaction; ASA = acetylsalicylic acid; EMG = electromyogram.

Table 2. *Comparison of characteristics of the dataset*

Characteristic	HMG-CoA-reductase inhibitor	Other drugs in the database
Mean age (years)	59.7	53.4
Gender (%)		
• Male	52.4	36.5
• Female	47.6	63.5
Use of concomitant antidiabetic medication (%)		
• Yes	10.0	5.3
• No	89.7	94.7

Table 3. *Reporting odds ratio (ROR) for HMG-CoA-reductase inhibitors in World Health Organisation database*

ADR associated with HMG-CoA-reductase inhibitors	Number of reports	ROR (95% CI)
Neuropathy	245	1.53 (1.34-1.73)
Peripheral neuropathy	469	5.05 (4.59-5.56)
Polyneuropathy	17	4.85 (2.94-8.01)
Total	*731*	*2.86 (2.66-3.09)*

Collaborating Centre for International Drug Monitoring in Uppsala, Sweden[#]. This database contains 733 ADRs of neuropathy, peripheral neuropathy or polyneuropathy, which are disproportionately associated with the use of HMG-CoA-reductase inhibitors. The unadjusted ROR of all HMG-CoA-inhibitors and the combined ADRs was 2.86 (95% CI: 2.66 to 3.09). *Table 3* provides an overview of the reports of the different associations.

DISCUSSION

The Netherlands Pharmacovigilance Centre Lareb received 17 reports of neuropathy and two reports of aggravation of polyneuropathy associated with the use of HMG-CoA-reductase inhibitors.

When considering the plausibility of a causal relationship between the reported neuropathy and the use of HMG-CoA-reductase inhibitors several aspects of the reports play a role, for example the time relationship (latency period, dechallenge or rechallenge), the presence of additional factors (underlying indication of the drug, medical history of the patient), the use of concomitant medication and diagnostic confirmation of the symptoms.

Because the cases in the Lareb database are reported on a voluntary basis they sometimes lack information about the above-mentioned characteristics. Several cases lack information about diagnostic confirmation of the reported symptoms, some patients suffer from diseases that might have contributed to the symptoms: renal failure (H), vitamin B12 deficiency (J), diabetes mellitus (Q and T), and finally the indication (hyperlipidaemia) itself might have induced neuropathy.[14] However, other characteristics of the reports, such as the disappearance of or improvement in the symptoms in seven cases and the relatively long latency period of the reports, support a causal relationship between the symptoms and the use of the HMG-CoA-reductase inhibitors. The long mean time to onset of the neurological symptoms described in reports in the Lareb database is in line with several other studies, supporting the suggestion that especially long-term exposure to HMG-CoA-reductase inhibitors increases the risk of neuropathy. The disappearance of the symptoms after discontinuation of HMG-CoA-reductase inhibitors in eight cases supports a relationship with the use of these drugs.

The exact mechanism by which HMG-CoA-reductase inhibitors can cause neuropathy is still unknown. Since neuropathy has been associated with the use of all HMG-CoA-reductase inhibitors, it appears to be a group effect. Several hypothetical theories about the possible mechanism have been postulated. Firstly, cholesterol is an important component of human cell membranes and therefore HMG-CoA-reductase inhibitors may, by inhibition of the cholesterol synthesis, change the function of nerve membranes.[6] Furthermore it has been suggested that in addition to the cholesterol-lowering effect, a decrease in the level of ubiquinone (coenzyme-Q) may also occur. Ubiquinone is involved in the mitochondrial respiratory chain, which in turn is responsible for the energy production of neurons and striated muscle.[6,11] Both theories could explain structural and functional alterations of the neurons associated with long-term exposure to HMG-CoA-reductase inhibitors.[6]

CONCLUSION

HMG-CoA-reductase inhibitors are used for primary and secondary prevention atherosclerosis. Treatment with HMG-CoA-reductase inhibitors significantly reduces the risk of cardiovascular morbidity and mortality. Polyneuropathy is a very rare side effect of HMG-CoA-reductase inhibitors. Long-term treatment with these drugs increases the risk of polyneuropathy. Considering the increasing number of patients using HMG-CoA-reductase inhibitors and the irreversibility of polyneuropathy, health care professionals should be aware of a possible role of HMG-CoA-reductase inhibitors in neuropathy. Additional research, including electromyography, may be useful.

[#]The views expressed are purely those of the writer and may not in any circumstances be regarded as stating an official position of WHO.

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