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HMG-CoA-reductase inhibitors and neuropathy

Introduction

HMG-CoA reductase inhibitors (statins) lower both the total cholesterol level and the LDL-cholesterol level. The HMG-CoA-reductase inhibitors are competitive inhibitors of the enzyme 3-hydroxy-3-methylglutargyl coenzyme A reductase, an enzyme that is of major importance in the synthesis of cholesterol. As a group the HMG-CoA reductase inhibitors are, combined with dietary measures, indicated for hypercholesterolemia. They are effective in both the primary and secondary prevention of coronary disease and stroke prevention [1].
Gastrointestinal complaints are the most frequently reported adverse reactions of HMG-CoA-reductase inhibitors. Elevation of the liver-enzymes (up to more than three times the upper normal level) and myopathy, including myositis and rhabdomyolysis, are the two most severe adverse drug reactions of the HMG-CoA- reductase inhibitors [2-6]. Patient deaths due to rhabdomyolysis resulted in the withdrawal of cerivastatin.

Peripheral neuropathy is a general term which includes a variety of conditions characterised by paraesthesias, sensory loss, muscle weakness, and hyperaesthesias of the extremities. The back-ground incidence (age- and sex-adjusted) for peripheral neuropathy not associated with alcohol or diabetes is 1.5 cases per 10,000 person-years (95% CI 0.9 - 2.3). The back-ground incidence (age and sex-adjusted) for diabetic polyneuropathy is 5.4 cases per 10,000 person-years (95% CI 3.3 - 8.3) [7].

Peripheral neuropathy is mentioned in the SPC of atorvastatin (Lipitor®) as an uncommonly (0.1-1%) occurring adverse reaction [5]. The SPC of simvastatin (Zocor®) mentiones peripheral neuropathy as an adverse reaction, which occurred in non-controlled trials and post-marketing surveillance [2]. SPC's of the other HMG-CoA-reductase inhibitors do not mention (peripheral) neuropathy as a possible adverse drug reaction.

Reports

On March 8 2004 the database of the Netherlands Pharmacovigilance Centre Lareb contained ten reports of neuropathy, expressed as neuropathy, peripheral neuropathy or polyneuropathy, in association with the use of HMG-CoA-reductase inhibitors. In addition to these reports the database contained 26 reports of paraesthesias, one report of sensory loss, 22 reports of muscle weakness and no reports of hyperaesthesias, conditions that might be a symptom of neuropathy.

From the ten reports of neuropathy, five concerned simvastatin, three pravastatin and two atorvastatin. In four cases the suspect HMG-CoA-reductase inhibitor has been discontinued and in these cases the patient (partially) recovered. The mean time to onset is 25.5 months (range 0.75 to 72 months).
Table 1 shows an overview of all reports concerning neuropathy, peripheral neuropathy and polyneuropathy associated with the use of HMG-CoA-reductase inhibitors.

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

sex, age	drug, dosage	concomitant medication	suspected adverse drug reaction	time to onset, outcome	remarks
A, M, 25	simvastatin, 1 dd 10 mg	Not reported	neuropathy, paraesthesia of arms and legs	8 months, recovered after withdrawal	
B, V, 59	simvastatin, 1 dd 20 mg	enalapril, labetalol	neuropathy peripheral	2 years, not recovered after withdrawal	
C, M, 56	atorvastatin, 1 dd 20 mg	acetylsalicylic acid	neuropathy peripheral of the knees and hands	5 months, almost completely recovered after withdrawal	
D, M, 65	pravastatin, 1 dd 10 mg	lansoprazole, oxazepam, acetylsalicylic acid	polyneuropathy of the legs	2 years, recovered after withdrawal	
E, V, 69	simvastatin, 1 dd 20 mg	not reported	neuropathy e.c.i.	3 weeks, unknown	
F, M, 71	Pravastatin, 1 dd 40 mg	lisinopril, budesonide, acetylsalicylic acid	pain and burning lower right leg and foot (at night)	5 years, recovering after withdrawal	
G, M, 77	simvastatin, 1 dd 40 mg; Sulfametho-xazol/ Trime thoprim, 2 dd 960 mg	tamsulosin, omeprazole, amiodarone, amlodipine, furosemide, acenocoumarol, spironolacton, quinapril, prednisolon, triamterene/ hydrochloro-thiazide	polyneuropathy, hepatitis, myositis, renal failure	1 year, unknown	EMG confirmed neuropathy
H, M, 52	simvastatin, 1 dd 10 mg	phenytoin	anoxal polyneuropathy	4 year, unknown	epilepsia
I, M, ?	Atorvastatin, ?	dipyramidol, enalapril/ hydrochloro-thiazide, folic acid, acetylsalicylic acid	neuropathy peripheral, cramps in extremities, muscle weakness of the legs	6 years, one month after withdrawal not recovered yet	chronic Vit. B12 deficiency
J, M, 64	pravastatin, 1 dd 40 mg	amlodipine, losartan, sotalol, acetylsalicylic acid	polyneuropathy	3 weeks, not recovered	dose reduced

Other sources of information

Literature

According to Backes and Howard [8], two epidemiologic studies and several case reports (with a total of 15 patients) have demonstrated a possible increased risk of peripheral neuropathy in patients using HMG-CoA-reductase inhibitors [8].

Jacobs [9] described a case of peripheral neuropathy in a patient treated with lovastatin and pravastatin. A 47-year-old woman with hypercholesterolemia experienced sensory neuropathy within two years after starting with lovastatin 20 mg daily. After discontinuation of lovastatin she recovered within eight weeks. After starting with pravastatin 20 mg daily she developed within two weeks progressive paraesthesias of the extremities, which diminished within four weeks after discontinuation of pravastatin [9].

Gaist *et al.* performed a population-based study to determine the relative risk of idiopathic polyneuropathy in patients receiving HMG-CoA-reductase inhibitors. Among non-exposed people of 50 years or older in the back-ground population the incidence of idiopathic polyneuropathy was 1.7 per 10,000 person-years among the non-exposed. The estimated odds ratio of idiopathic polyneuropathy among users of HMG-CoA-reductase inhibitors was 3.7 (95% CI 1.8 - 7.6), resulting in an incidence of 4.5 per 10,000 person-years
Long-term (more than two years) exposure to HMG-CoA-reductase inhibitors increases the risk for polyneuropathy [10].
These findings do not support the results of another study conducted by the same authors [11]. This study reported similar rates of neuropathy in nontreated lyperlipidemic patients and patients in the general population. However, because of the wide confidence intervals the results of this study are inconclusive and should be carefully interpreted [11].

Databases

On March 8 2004, the Lareb database contained 2259 possible ADRs during the use of HMG-CoA-reductase inhibitors, including the above mentioned ten cases of neuropathy. The reporting Odd's ratio (adjusted for diabetes mellitus to exclude confounding by indication) among patients older than 40 years was 3.4 (95% CI 1.6 - 6.9), indicating that neuropathy for HMG-CoA-reductase inhibitors is disproportionally present in the Lareb database.

The database of the WHO contained 62,164 ADRs associated with the use of HMG-CoA-reductase inhibitors, including cerivastatin. A total of 624 ADRs concern a neuropathy (expressed as neuropathy, peripheral neuropathy and polyneuropathy), which is disproportionally present in the database. From these ADRs 237 concern neuropathy, 381 peripheral neuropathy and six polyneuropathy. Table 2 shows an overview of reporting odds ratio's of these associations.

Table 2. Reporting Odds Ratio WHO database

ADR associated with HMG-CoA-reductase inhibitors	**Number of reports**	**ROR (95% CI)**
Neuropathy	237	1.15 (1.01 - 1.30)
Peripheral neuropathy	381	5.11 (4.60 - 5.68)
Polyneuropathy	6	3.59 (1.56 - 8.22)
Total	**624**	**2.21 (2.04 – 2.40)**

Mechanism

The exact mechanism by which HMG-CoA-reductase inhibitors might cause neuropathy is still unknown yet. It has been suggested that HMG-CoA-reductase inhibitors, in addition to the cholesterol-lowering effect, decrease the level of ubiquinone (coenzyme-Q) also. Ubiquinone is

involved in the mitochondrial respiratory chain, which in turn is responsible for the energy utilization of neurons and striated muscle [8]. Recently, it has been suggested that a negative effect of HMG-CoA-reductase inhibitors on the selenoprotein synthesis might explain why HMG-CoA-reductase inhibitors can induce myopathy [12]. It is not clear whether this hypothesis also explains neuropathy due the HMG-CoA-reductase inhibitors.

Conclusion

Neuropathy is a known ADR of atorvastatin (Lipitor®) and simvastatin (Zocor®) and might theoretically be explained by the pharmacological properties of HMG-CoA-reductase inhibitors. Long-term exposure to HMG-CoA-reductase inhibitors increases the risk for neuropathy. Ten cases in the database Lareb of neuropathy associated with the use of HMG-CoA-reductase inhibitors with a mean time to onset of 25.5 months support this.

References

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