

Concurrent use of verapamil or diltiazem and HMG-CoA reductase inhibitors increases the risk of muscle related ADRs

Introduction

The HMG-CoA reductase inhibitors (statins) are effective in both the primary and secondary prevention of ischaemic heart disease. As a group, these drugs are well tolerated apart from two uncommon but potentially serious adverse effects: elevation of liver enzymes and skeletal muscle abnormalities, which range from benign myalgias to life-threatening rhabdomyolysis [1-6]. The recent withdrawal of cerivastatin as a result of deaths from rhabdomyolysis illustrates the clinical importance of such interactions.

Most statins are metabolised by the cytochrome P450 (CYP) enzyme system. The CYP3A4 iso-enzyme metabolises lovastatin, simvastatin, atorvastatin and cerivastatin, whereas CYP2C9 metabolises fluvastatin. Pravastatin and rosuvastatin are not significantly metabolised by the CYP system. [1-6].

The calcium channel blockers verapamil and diltiazem are inhibitors of CYP3A4, but also substrate.

Co-administration of a statin -especially lovastatin, simvastatin, atorvastatin and cerivastatin- and verapamil or diltiazem may therefore increase the statin concentration and result in muscle pathology [7].

The Dutch SPC of diltiazem mentions inhibition of cytochrome P450 but the specific warning for increased blood levels is limited to cyclosporine, carbamazepine and theophylline; statins are not mentioned [8].

The Dutch SPCs of verapamil does not mention the inhibition of cytochrome P450. Nevertheless, it warns for blood level changes of cyclosporine, carbamazepine and theophylline, but not statins [9].

Reports

The Lareb database contains 41 reports with muscle related ADRs during use of a statin combined with verapamil or diltiazem, as illustrated by two cases.

Patient A is a 63-year-old male used simvastatin 40 mg chronically. Diltiazem was started, and the dosage simvastatin was reduced (20 mg) due to the potential interaction. Nevertheless, he developed myalgia and simvastatin was discontinued. Myalgia disappeared. Creatinine kinase (CPK) levels were not determined.

Patient B concerns a 77-year-old female. Four months after starting simvastatin, indicated for hypercholesterolaemia, and one month after addition of diltiazem, she developed rhabdomyolysis. CPK levels were not reported. Simvastatin was discontinued, but she had not yet recovered at the moment of notification. Concomitant medication included paroxetine, metoprolol, folic acid and low dose aspirin. Although paroxetine is a weak CYP3A4 inhibitor, and aspirin may induce CYP3A4 activity in healthy subjects, the chronic use of these preclude significant influence [10,11].

Other sources of information

Literature

The effect of diltiazem on the pharmacokinetics of simvastatin was studied in 10 healthy adults. The serum concentration of simvastatin was significantly increased (AUC by 4.8 +/- 1.7-fold, an increase in maximum concentration (C_{max}) by 4.1 +/- 1.8-fold, and an increase in half-life by 2.4 +/- 1.7-fold, without affecting the time to reach C_{max}) with concurrent use of diltiazem via inhibition of cytochrome P450 3A4-mediated metabolism [12].

A pharmacokinetic study involving 12 healthy volunteers showed that verapamil increased the mean C_{max} of simvastatin by 2.6-fold and the AUC from 0 to 24 hours by 4.6-fold [13].

databases

The association between statins combined with diltiazem or verapamil and muscle ADRs is not statistically significant disproportional in the Lareb database.

Table 1: Diltiazem and statins: number of Lareb reports on muscle related ADRs

	Myalgia, muscle pain, muscle ache	Rhabdomyolysis	Myopathy, muscle weakness	Other	Total
atorvastatin	6	0	1	1	8
cerivastatin	2	0	0	0	2
simvastatin	11	3	1	2	17
fluvastatin	5	0	2	0	7
pravastatin	1	0	0	2	3
total	25	3	4	5	37

Table 2: Verapamil and statins: number of Lareb reports on muscle related ADRs

	Myalgia, muscle pain, muscle ache	Rhabdomyolysis	Total
atorvastatin	1	0	1
fluvastatin	1	0	1
simvastatin	1	1	2
total	3	1	4

Mechanism

The theoretical mechanism is explained in the introduction. In clinical practice, the risk of a serious interaction causing myopathy is enhanced when statin metabolism is markedly inhibited [14].

Conclusion

Co-administration of a statin, that is metabolised by CYP3A, with verapamil or diltiazem as CYP3A4-inhibitors may result in clinically significant muscular ADRs, including rhabdomyolysis.

References

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