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Frequency and Clinical Relevance of Drug Interactions with Lovastatin and Simvastatin

An Observational Database Study

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Abstract

Background: Concomitantly used cytochrome P450 (CYP) 3A4 inhibitors and inducers have been shown to alter the plasma concentrations of the HMG-CoA reductase inhibitors ('statins') lovastatin and simvastatin. Myopathy is a serious adverse effect of statins. Concurrent use of statins with fibrates in particular seems to increase the risk of this adverse effect.

Objective: To evaluate the incidence and clinical consequences of the use of lovastatin or simvastatin with concomitant CYP3A4 inhibitors and inducers, and with fibrates.

Methods: An observational database study of hospitalized patients treated in Turku University Hospital, Turku, Finland, covering the period 1 July 1996 to 30 June 2003, and of nationwide community data from the Finnish Prescription Register over the period 1 April to 30 June 2001 was conducted. In the hospital setting, the study population comprised 71 025 patients (93 467 treatment periods) over 7 years, with a total of 5320 treatment periods of lovastatin or simvastatin. The community-based, nationwide survey included all reimbursed prescriptions of lovastatin and simvastatin (n = 91 656) in Finland during a 3-month period. The frequency of drug-drug interactions involving lovastatin or simvastatin was studied. The efficacy and safety of the various statin/concomitant drug combinations was estimated by evaluating patients' laboratory data.

Results: Concomitant use of lovastatin or simvastatin with interacting medication was detected in 13.3% (704) and 6.9% (6338) of patients in hospital and community settings, respectively. Co-administration of lovastatin or simvastatin with CYP3A4 inhibitors or inducers did not have a clinically significant effect on serum lipid values. Plasma creatine kinase (CK) activity was significantly higher in patients receiving a statin and a fibrate compared with a statin only (433 U/L vs 209 U/L, p = 0.053). Co-administration of a statin and a CYP3A4 inhibitor did not increase CK activity.

Conclusion: Although the pharmacokinetic interactions between lovastatin or simvastatin and CYP3A4 inhibitors and inducers are substantial, their clinical relevance seems to be limited, at least with lower statin doses. However, combining statins with fibrates, especially gemfibrozil, clearly increases the potential for muscular toxicity.

Introduction

HMG-CoA reductase inhibitors ('statins') are among the most widely used drugs in the Western world. They effectively lower serum cholesterol levels and reduce cardiovascular morbidity and mortality. The use of statins is, however, complicated by rare, but often serious, muscular adverse effects such as myalgia, serum creatine kinase (CK) elevation and rhabdomyolysis.[1-3] Recently, statin-induced muscular adverse effects and drug interactions received wide attention, as cerivastatin was withdrawn from the market after causing several cases of fatal rhabdomyolysis, particularly when co-administered with gemfibrozil.[4,5] The exact mechanism of statin-induced muscular toxicity and the reason why it is aggravated by the co-administration of fibrates are not clear, but pharmacodynamic synergistic toxicity has been suggested. In 2002 it was reported that concentrations of cerivastatin in plasma are clearly elevated (by about 6-fold) when the drug is co-administered with gemfibrozil, due to the reduction in plasma clearance of cerivastatin by the cytochrome P450 (CYP) 2C8 enzyme.[6] Thus, pharmacokinetic interactions may also contribute to the toxicity.

Several phase I clinical trials have shown that strong CYP3A4 inhibition increases the area under the concentration-time curve (AUC) of lovastatin and simvastatin by 10- to 15-fold.[7,8] Both drugs undergo extensive CYP3A4-dependent first-pass metabolism, which makes them particularly vulnerable to metabolism-based drug interactions.[9,10] Induction of CYP3A4 with, for example, rifampicin or carbamazepine reduces simvastatin concentrations by 87% and 75%, respectively.[11,12] It is generally assumed that the several-fold alterations of lovastatin or simvastatin concentrations caused by metabolism-based drug interactions could affect their efficacy and safety, but very little is actually known about the clinical relevance of these interactions. The aims of this epidemiological database study were to investigate the frequency of drug-drug interactions with lovastatin and simvastatin, both in the community and hospital settings, and to estimate the clinical consequences of these interactions.

Methods

Interacting Drugs

The drugs with the potential to interact with lovastatin and simvastatin were identified by literature searches in the MEDLINE database. Eight well known CYP3A4 inhibitors (clarithromycin,[13,14] ciclosporin,[15-17] diltiazem,[18-20] erythromycin,[21,22] itraconazole,[7,8,23] ketoconazole,[24] nefazodone,[25-27] verapamil[21]), five CYP3A4 inducers (carbamazepine,[12] phenobarbital,[28,29] phenytoin,[28,30] rifabutin,[28,31] rifampicin[11]) and three fibrates (bezafibrate,[28,32] clofibrate,[28,32] gemfibrozil[33-35]) were included in the study.

Study Population

The hospital-based study population consisted of 71 025 patients (93 467 successive treatment periods) treated in the internal medicine, pulmonary medicine and neurology wards at Turku University Hospital, Turku, Finland, during a 7-year period (from 1 July 1996 to 30 June 2003).

The community-based study population included all patients who received reimbursed prescriptions for lovastatin or simvastatin (n = 91 656) during a 3-month study period in the year 2001. The prescriptions were identified in the prescription register of the Social Insurance Institution (SII), which covers 97% of reimbursed prescriptions of permanent residents of Finland.

Searches in the Hospital Medication Database

From the beginning of 1996, complete information on the medication of all patients treated on the hospital wards has been prospectively recorded into an electronic UNIX®-based database in Turku University Hospital. The data from the medication database contain the following information: social security number identifying the patient; name, strength and dosage form of the drug; administered dosage of the drug; starting date of the medication and ward; cessation date of the medication and ward.

Co-administration of lovastatin or simvastatin with the chosen CYP3A4 inhibitors, CYP3A4 inducers or fibrates was searched for in this medication database. The study patients were divided into four study groups: patients receiving lovastatin or simvastatin with (i) a CYP3A4 inhibitor; (ii) a CYP3A4 inducer; (iii) a fibrate (the interaction groups); and (iv) those receiving either statin but none of the interacting drugs (the control group). The results are given for pooled data for the lovastatin and simvastatin groups (i.e. both statin groups combined). Patients receiving both a CYP3A4 inhibitor and an inducer were excluded. Those who received a CYP3A4 inhibitor or inducer concomitantly with a statin/fibrate combination were included in the fibrate group. Concomitant use was considered as a potential interaction and was included in the frequency analysis if the co-administration of the drug pair lasted for at least 2 days.

The searches were based on the Anatomical Therapeutic Chemical (ATC) codes, established and updated by the WHO.[36] Only the codes for drugs to which systemic exposure had occurred, (i.e. excluding topical administration) were included in the searches. The personnel of the wards were not aware of the study. The searches were performed according to the study protocol approved by the local authorities responsible for the hospital registers.

Searches in the Hospital Laboratory Database

Routinely collected laboratory data that were also recorded in the hospital database were used as the source of information on the efficacy and safety of each patient's treatment. The effect of the potential drug-drug interaction on the efficacy of statin treatment was analysed using data for fasting plasma (FP) concentrations of total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides, as well as the HDL-cholesterol/total cholesterol ratio. The activities of CK, ALT and γ-glutamyl transferase (γGT) in plasma served as a proxy for safety evaluation. The searches in the laboratory database were performed with automatic data processing codes for laboratory tests. A minimum of 7 days' exposure to the potential drug-drug interaction was required for inclusion into the efficacy and safety analyses. In the case of several measurement values during the period of exposure, the average of the values was used.

Searches in the Prescription Register of the Social Insurance Institution

The frequency of potential drug-drug interactions in patients treated with lovastatin or simvastatin in the community setting was estimated from the prescription register of the SII. The survey included all reimbursed prescriptions for lovastatin and simvastatin during a 3-month window between 1 April and 30 June 2001. The patients who had a reimbursed prescription for a CYP3A4 inhibitor (clarithromycin, ciclosporin, diltiazem, erythromycin, itraconazole, ketoconazole or verapamil), for a CYP3A4 inducer (carbamazepine or phenytoin) or a fibrate (bezafibrate or gemfibrozil) during the same time period were considered to be exposed to a drug-drug interaction. The 3-month period was chosen because it covers the maximum quantity of drugs for which patients can be reimbursed in one transaction.

Statistical Analyses

In the hospitalized patients, between-group differences in sex distribution were tested using the chi-squared test. Mean doses, efficacy and safety laboratory values were compared between the groups using one-way ANOVA followed by Dunnett's test when the interaction groups were compared with the control group. Efficacy and safety laboratory values were also compared between the groups with analysis of covariance (ANCOVA)

Table I. Demographic characteristics of the hospitalized patients

Interaction group	Treatment periods (% of total)	Patients (% of total)	Male/female	Mean age (range)
CYP3A4 inhibitor	468 (8.8)	442 (8.4)	266/202**	64 (23–89)
CYP3A4 inducer	207 (3.9)	193 (3.7)	133/74	67* (42–88)
Fibrate	69 (1.3)	69 (1.3)	47/22	61* (43–80)
Control	4576 (86.0)	4572 (86.7)	2978/1598	64 (16–95)

CYP = cytochrome P450; * $p < 0.05$, ** $p < 0.001$ compared with control.

after adjustment for age, sex and mean dose. Because of positively skewed distribution, triglyceride values were log-transformed before analysis. Logistic regression analysis was used for between-group comparison of the risk being outside the target range of the laboratory values. Multivariate logistic regression analysis was used to adjust for age, sex and mean drug dose. The control group was the reference group in the logistic models. The risk of being outside the target range is presented as an odds ratio (OR) and its 95% confidence interval. Statistical analysis was performed with SAS System for Windows, release 9.1 (SAS Institute Inc., Cary, NC, USA). p-Values <0.05 were considered statistically significant.

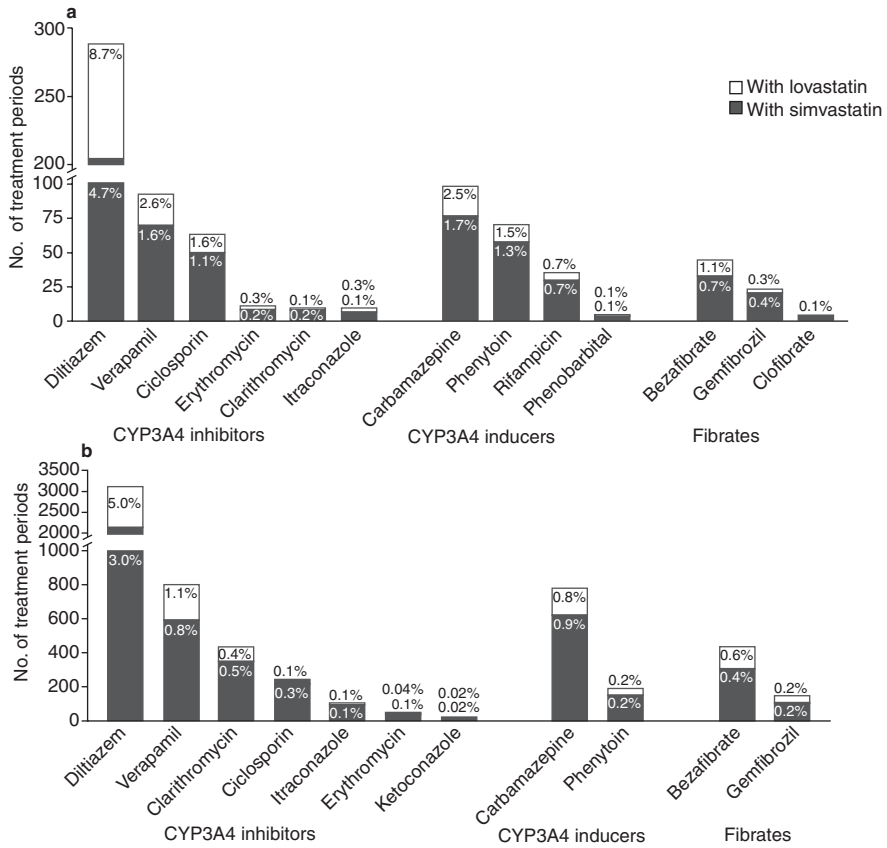

Fig. 1. Incidence of concomitant use of cytochrome P450 (CYP) 3A4 inhibitors, CYP3A4 inducers or fibrates with lovastatin and simvastatin in (**a**) hospitalized patients and (**b**) community-based patients. The percentages represent the proportion of concomitant use vs total use of each statin.

Target values for laboratory determinations, valid in Finland in 1999 (i.e. mid-point of the study period), were as follows: FP total cholesterol <5.0 mmol/L; FP triglyceride <2.0 mmol/L; FP HDL cholesterol >1.0 mmol/L for men, >1.2 mmol/L for women; HDL-cholesterol/total cholesterol ratio >25%; FP LDL-cholesterol <3.5 mmol/L; plasma CK<285 U/L for men, <165 U/L for women; plasma γGT <90 U/L for men, <75 U/L for women; plasma ALT <60 U/L for men, <45 U/L for women.

Results

Frequency of Drug-Drug Interactions

Among the 93 467 hospital treatment periods included in the study during the 7-year period, lovastatin or simvastatin was used in 5320 treatment periods; the statin most often used (83.6%) was simvastatin (4447 treatment periods). Lovastatin or simvastatin was used concomitantly with a CYP3A4 inhibitor in 468 treatment periods (8.8% of all statin treatment periods), a CYP3A4 inducer in 207 treatment periods (3.9%) and a fibrate in 69 treatment periods (1.3%). Thus, from the hospitalized patients receiving either simvastatin or lovastatin, 13.4% were exposed to a potential statin drug interaction (table I). The most common CYP3A4 inhibitor, CYP3A4 inducer and fibrate given together with either of the statins were diltiazem (5.3% of all statin treatment periods), carbamazepine (1.8%) and bezafibrate (0.8%), respectively (figure 1a).

The nationwide prescription register indicated that, among the 5.2 million inhabitants in Finland, 19 632 patients received reimbursed lovastatin and 72 024 patients received reimbursed simvastatin during the 3-month study period. Lovastatin or simvastatin was used concomitantly with a CYP3A4 inhibitor in 4791 cases (5.2% of all statin-treated patients), a CYP3A4 inducer in 966 cases (1.0%) and a fibrate in 581 cases (0.6%). Thus, altogether 6338 patients (6.9%) taking simvastatin or lovastatin were potentially exposed to a drug interaction. Diltiazem (3.4% of statin prescriptions), carbamazepine (0.8%) and bezafibrate (0.5%) were the most commonly co-administrated CYP3A4 inhibitor, CYP3A4 inducer and fibrate, respectively, among patients prescribed either simvastatin or lovastatin (figure 1b).

Characteristics of Hospitalized Patients Taking Simvastatin or Lovastatin

The mean age of the hospitalized patients taking a statin only, without an interacting drug, was 64 years (range 16–95 years), whereas patients receiving a fibrate together with a statin were younger (mean age 61 years, range 43–80 years; $p = 0.040$), and those receiving a CYP3A4 inducer with a statin were older (67 years, range 42–88 years; $p = 0.008$). Women were more likely to have a potential interaction when taking a statin than men (OR 1.2; 95% CI 1.1, 1.5), but otherwise the demographic characteristics did not differ between the study groups (table I).

The mean (± SD) daily dose of simvastatin was 15.4 ± 7.9 mg in patients receiving no interacting drugs; the dose was higher in patients also receiving a fibrate (22.4 ± 15.7 mg; $p < 0.001$) and slightly lower in patients taking a CYP3A4 inhibitor (14.0 ± 6.3 mg; $p = 0.004$). The mean (± SD) daily dose of lovastatin varied between 22.1 ± 6.5 mg (patients also receiving a CYP3A4 inducer) and 30.0 ± 19.1 mg (patients taking a fibrate) with no statistically significant difference between the study groups.

Lipid Concentrations in Plasma

When compared with the group using a statin without any potentially interacting drug, all other groups had higher total plasma cholesterol levels. For patients using a CYP3A4 inhibitor or inducer, this difference was explained by significantly higher HDL-cholesterol levels; no significant differences were seen between these groups and the control group in the HDL-cholesterol/total cholesterol ratio. However, in patients receiving a fibrate in addition to a statin, both the HDL-cholesterol/total cholesterol ratio and HDL-cholesterol level were significantly lower than in the control group. LDL-cholesterol levels were essentially similar in all study groups. Levels of triglycerides were constantly higher in fibrate-treated patients than in patients receiving a statin without an interacting drug. Adjustment for gender, age, statin used and statin dose did not

Table II. Effects of lovastatin or simvastatin alone (control) and in co-administration with cytochrome P450 (CYP) 3A4 inhibitors, CYP3A4 inducers or fibrates on plasma lipid profile

Interaction group	FP cholesterol (mmol/L)	FP HDL-cholesterol (mmol/L)	HDL-cholesterol/total cholesterol ratio (%)	FP LDL-cholesterol (mmol/L)	FP triglycerides (mmol/L)
CYP3A4 inhibitor					
Mean ± SD	5.0 ± 1.1**†	1.32 ± 0.42*†	27 ± 9	2.9 ± 0.8	1.8 ± 1.3
Range	2.1–11.0	0.48–3.53	10–55	1.0–6.3	0.3–19.5
n	323	319	316	314	324
CYP3A4 inducer					
Mean ± SD	5.2 ± 1.1**‡	1.43 ± 0.52**‡	28 ± 9	3.0 ± 0.9*†	1.6 ± 0.8
Range	3.1–12.4	0.50–3.12	13–54	1.4–8.0	0.4–4.8
n	115	116	112	111	118
Fibrate					
Mean ± SD	5.4 ± 1.1**†	1.04 ± 0.32**‡	20 ± 5**‡	3.0 ± 0.9	3.2 ± 2.4**‡
Range	3.7–8.8	0.51–2.14	10–30	1.3–5.2	0.8–14.8
n	55	56	55	52	56
Control					
Mean ± SD	4.8 ± 1.0	1.25 ± 0.35	27 ± 7	2.8 ± 0.9	1.6 ± 0.9
Range	2.0–12.8	0.10–3.20	3–64	0.5–26.5	0.2–12.8
n	3150	3136	3117	3083	3146

FP = fasting plasma; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; * $p < 0.05$, ** $p < 0.001$ compared with control (univariate analysis, one-way ANOVA); † $p < 0.05$, ‡ $p < 0.001$ compared with control (multivariate analysis, analysis of covariance [ANCOVA] adjusted for age, sex and mean dose).

change the interpretation of the statistical analyses (table II).

The target concentration for total cholesterol (<5.0 mmol/L) was reached by 60.8% of control patients, whereas the outcome was poorer in patients who received concomitantly either a CYP3A4 inducer or a fibrate; compared with the control group, the risk of being above the target value was increased by 2.3- and 2.1-fold, respectively. The HDL-cholesterol level was within the target range in 69% of the control group and in 79% ($p = 0.012$ vs control) of patients also receiving a CYP3A4 inducer (OR 0.6; 95% CI 0.4, 0.9). The opposite was seen among fibrate users, who had a clearly elevated risk of being outside the target range of HDL-cholesterol (OR 3.8; 95% CI 2.2, 6.6). Patients in the fibrate group had about a 13-fold higher risk of having their triglyceride level above target (OR 13.5; 95% CI 6.7, 27.2). Also, HDL-cholesterol/total cholesterol ratios and LDL-cholesterol values were more often outside the target in fibrate users (OR 6.7, 95% CI 3.1, 14.5; OR 2.0, 95% CI 1.1, 3.6, respectively) [table III].

Biochemical Safety Indicators

In the group receiving both a fibrate and a statin, the mean plasma CK activity was more than twice (433 U/L vs 209 U/L; $p = 0.010$) that of the group treated with a statin only, but in the multivariate analysis, the difference reached only a borderline statistical significance ($p = 0.053$). The OR for elevation of CK activity above the target value (<285 U/L for men, <165 U/L for women) was 2.0 for the fibrate group compared with the statin-only patients (95% CI 1.0, 4.0). Interestingly, the elevation of plasma CK was much stronger in the gemfibrozil-exposed patients (mean 711 U/L) than in the bezafibrate-exposed patients (mean 251 U/L), but this finding did not reach statistical significance, because of the limited number of patients. Concomitant use of a CYP3A4 inhibitor resulted in a lower plasma CK activity when compared with patients receiving a statin alone (table IV and table V).

When compared with patients receiving a statin alone, the activity of plasma γGT was somewhat higher both among patients receiving a CYP3A4 inhibitor and among those receiving a CYP3A4 inducer, which was also reflected in a more common

Table III. The percentage of patients reaching the target plasma lipid concentration and the risk (odds ratio [OR] and 95% CI) for being outside the target concentration when exposed to lovastatin or simvastatin alone or in combination with cytochrome P450 (CYP) 3A4 inhibitors, CYP3A4 inducers or fibrates

Interaction group	FP cholesterol	FP HDL-cholesterol	HDL-cholesterol/total cholesterol ratio	FP LDL-cholesterol	FP triglycerides
CYP3A4 inhibitor					
Percentage	53.6	68.3	50.6	76.4	70.1
OR (95% CI)	1.23 (0.97, 1.57)	0.99 (0.77, 1.27)	1.14 (0.90, 1.45)	1.26 (0.95, 1.67)	1.30* (1.01, 1.69)
CYP3A4 inducer					
Percentage	43.5	79.3	50.9	76.6	77.1
OR (95% CI)	2.25** (1.52, 3.33)	0.56* (0.36, 0.89)	1.17 (0.79, 1.72)	1.37 (0.86, 2.16)	1.00 (0.64, 1.55)
Fibrate					
Percentage	38.2	37.5	14.6	63.5	17.8
OR (95% CI)	2.07* (1.17, 3.67)	3.79** (2.18, 6.57)	6.72** (3.11, 14.5)	2.01* (1.11, 3.64)	13.5** (6.74, 27.2)
Control					
Percentage	60.8	68.1	54.2	81.2	76.1

FP = fasting plasma; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; * $p < 0.05$, ** $p < 0.001$ compared with control (multivariate logistic regression, adjusted for age, sex and mean dose).

occurrence of γGT activities outside the target range in these groups when compared with controls (OR 1.4, 95% CI 1.0, 2.0; OR 4.6, 95% CI 3.1, 6.8, respectively). In the multivariate analysis, there were no between-group differences in the mean plasma ALT activities, but values above the target range were seen more often in patients receiving a CYP3A4 inhibitor than in control patients (OR 1.6; 95% CI 1.1, 2.2) [table IV and table V].

Table IV. Effects of lovastatin or simvastatin alone (control) and in co-administration with cytochrome P450 (CYP) 3A4 inhibitors, CYP3A4 inducers or fibrates on the activities of plasma creatine kinase (CK), γ-glutamyl transferase (γGT) and ALT

Interaction group	Plasma CK (U/L)	Plasma γGT (U/L)	Plasma ALT (U/L)
CYP3A4 inhibitor			
Mean ± SD	146 ± 195**†	103 ± 42*	39 ± 76
Range	11–1314	7–2635	5–773
n	182	191	320
CYP3A4 inducer			
Mean ± SD	221 ± 442	110 ± 91**†	27 ± 21
Range	13–3435	10–593	5–172
n	78	124	160
Fibrate			
Mean ± SD	433 ± 1351*	80 ± 79	35 ± 29
Range	40–8971	10–342	9–128
n	43	39	58
Control			
Mean ± SD	209 ± 479	66 ± 97	33 ± 59
Range	5–10234	6–1273	3–1731
n	1517	1594	2996

* $p < 0.05$, ** $p < 0.001$ compared with control (univariate analysis, one-way ANOVA); † $p < 0.001$ compared with control (multivariate analysis, analysis of covariance [ANCOVA], adjusted for age, sex and mean dose).

Discussion

Our data indicate that co-administration of lovastatin and simvastatin with well established strong to moderate inhibitors or inducers of the CYP3A4 enzyme is common, both in hospitalized patients and in the community setting. However, based on laboratory data, the rate of adverse clinical consequences of these potential pharmacokinetic interactions is quite low. A totally different picture emerged when fibrates were used with statins; the risk of being above the normal range of CK activity was elevated 2-fold when compared with patients on a statin only.

In an earlier study investigating the occurrence of myopathy during statin treatment and its relationship with the use of CYP3A4 inhibitors, the incidence during simvastatin treatment was found to be only 0.025%, whereas that associated with the concomitant use of ciclosporin was higher.[37] No association with verapamil or diltiazem was noted, however.[37] Verapamil and diltiazem, both moderate CYP3A4 inhibitors, were the most frequently used inhibitors in our study (figure 1). This, together with the low incidence of clinically manifest muscle complications associated with statins and the low

Table V. Percentage of patients within the normal (target) range of enzyme activities and risk (odds ratio [OR] and 95% CI) of having creatine kinase (CK), γ-glutamyl transferase (γGT) and ALT activity above the normal range when exposed to lovastatin or simvastatin alone or in combination with cytochrome P450 (CYP) 3A4 inhibitors, CYP3A4 inducers or fibrates

Interaction group	Plasma CK	Plasma γGT	Plasma ALT
CYP3A4 inhibitor			
Percentage	85.2	74.4	85.9
OR (95% CI)	0.86 (0.56, 1.33)	1.43* (1.00, 2.04)	1.58* (1.12, 2.23)
CYP3A4 inducer			
Percentage	79.5	50.0	93.1
OR (95% CI)	1.29 (0.73, 2.28)	4.61** (3.13, 6.75)	0.80 (0.42, 1.49)
Fibrate			
Percentage	72.1	69.3	87.9
OR (95% CI)	2.02* (1.02, 4.04)	1.79 (0.88, 3.64)	1.20 (0.53, 2.71)
Control			
Percentage	83.5	81.4	91.2

* $p < 0.05$, ** $p < 0.001$ compared with control (multivariate logistic regression, adjusted for age, sex and mean dose).

statin dose used by our patients, may explain the apparent lack of clinically relevant interaction when the inhibitors were used together with statins. Nevertheless, our data reflect the real everyday use of statins and drugs interacting with them, increasing its relevance.

We noted that ciclosporin used together with a statin did not cause more elevations of plasma CK (n = 40 for ciclosporin) or transaminase (γGT: n = 45, ALT: n = 58) than other CYP3A4 inhibitors (p = 0.80, 0.79 and 0.17, respectively; data not shown). In several clinical studies, simvastatin has been well tolerated in transplant patients receiving ciclosporin, provided that the dose of simvastatin has been low, as was the case in our study.[38,39] Furthermore, it is likely that mechanisms other than CYP3A4 inhibition contribute to the muscular toxicity in statin-treated patients receiving ciclosporin.[37]

Compared with the control group, total cholesterol was somewhat higher in all statin groups receiving a potentially interacting medication. A closer analysis revealed that, in patients using either a CYP3A4 inhibitor or a CYP3A4 inducer, this difference could be explained by higher HDL-cholesterol values, whereas the LDL-cholesterol levels were similar and the ratio of HDL-cholesterol to total cholesterol remained unaffected.

Strong CYP3A4 inducers, like carbamazepine or rifampicin, have been shown to decrease exposure to simvastatin by 75–87%, and the same would be expected for lovastatin.[11,12] With this background, it is somewhat surprising that these strong pharmacokinetic interactions leading to marked decreases in lovastatin or simvastatin exposure seem to have rather little effect on the efficacy of statin treatment. One potential explanation could be that, after oral administration, the concentrations of these statins and their CYP3A4-dependent active metabolites formed during first-pass metabolism are still sufficiently high in the liver, the principal site of cholesterol synthesis, to induce a therapeutic effect. Furthermore, use of CYP3A4 inducing agents *per se* is associated with higher HDL-cholesterol levels in patients receiving long-term antiepileptic monotherapy, in particular carbamazepine.[40] Nevertheless, one isolated case report has been published that suggests that CYP3A4 induction could decrease the cholesterol-lowering effect of simvastatin.[41]

The strongest CYP3A4 inhibitors, such as itraconazole, increase the concentrations of lovastatin, simvastatin and their active metabolites by 10- to 20-fold.[7,8,23] Diltiazem, the most commonly used CYP3A4 inhibitor in our study, increases lovastatin and simvastatin concentrations about 3.5-fold.[18-20] However, despite this powerful potential increase in exposure to the statins, their lipid-lowering effects were not enhanced. Although our data suggest that, in the general population, drug interactions between moderate doses of lovastatin or simvastatin and CYP3A4 inhibitors and inducers may possess little clinical relevance, it is obvious that in some individual patients, having thus far unidentified predispos-

ing factors, these interactions may manifest in severe muscular toxicity.

Statin doses were higher in the fibrate groups when compared with other study groups, which may partly explain the increased muscular effects. In the present study, 69 patients received lovastatin or simvastatin together with a fibrate: 42 patients used bezafibrate, 23 gemfibrozil and 4 clofibrate. When comparing bezafibrate and gemfibrozil, the mean CK level was almost 3-fold higher in gemfibrozil-treated patients. It has been demonstrated that gemfibrozil, but not bezafibrate, increases concentrations of active acid forms of lovastatin and simvastatin in plasma, so the increased CK activities may have, at least partly, a pharmacokinetic origin.[33,42] Furthermore, combination therapy with lovastatin and clofibrate has been shown to be beneficial without adverse effects in patients with type III hyperlipoproteinaemia.[43]

Our study design was observational, which has some important limitations. There is the possibility of selection bias towards 'tolerant' patients, which may have led to an overestimation of the safety of the co-administration of the statins studied here with CYP3A4 inhibitors or fibrates. Since the medications were not allocated randomly to the patients, the co-morbidities and severity of the disease and other background variables of the subjects could not be controlled and may have affected the results. This is the most probable explanation for the high levels of total cholesterol in fibrate-treated patients. The physicians had probably started combination therapy with a statin and a fibrate particularly in patients with a severe or combined hyperlipidaemia. Although not absent, the risk for such confounding is much smaller when interpreting the statin/CYP3A4 inducer combination data on the therapeutic outcome. There is no reason to believe that the dyslipidaemia *per se* had affected the decision to include a CYP3A4 inducer into the therapy. It should be noted that the use of cardiovascular drugs such as diltiazem or verapamil may have caused selection bias towards more complicated states of hyperlipidaemia.

Based on the nationwide prescription register data, it can be assumed that more than 90 000 patients were treated with either lovastatin or simvastatin during the 3-month time window in 2001. Almost 7% of them (6338 patients) were exposed to drug treatment that had the potential to interact with the statins. Still, only six cases of rhabdomyolysis were reported in Finland during the 7-year time period covered by our study.[44] One of these cases was caused by simvastatin alone, without any interacting medication and all patients recovered.[44]

Conclusion

Of hospitalized patients and outpatients receiving lovastatin or simvastatin treatment in our observational study, 7–13% were exposed to a potentially interacting drug. However, drug interactions between these statins at low doses and inhibitors or inducers of CYP3A4 did not manifest themselves in adverse laboratory values, at least when moderate doses of statins were used. Adverse clinical consequences of interactions between lovastatin or simvastatin and fibrates appears to be much more frequent, and gemfibrozil in particular should be avoided in patients receiving lovastatin and simvastatin.

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