PHARMACOKINETICS AND DRUG DISPOSITION

Exposure of atorvastatin is unchanged but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy

**Background:** The most serious side effect from statin treatment is myopathy, which may proceed to rhabdomyolysis. This is the first study to investigate whether the pharmacokinetics of either atorvastatin or its metabolites, or both, is altered in patients with atorvastatin-related myopathy compared with healthy controls.

**Methods:** A 24-hour pharmacokinetic investigation was performed in 14 patients with atorvastatin-related myopathy. Relevant polymorphisms in **SLCO1B1** (encoding organic anion transporting polypeptide 1B1), **MDR1/ABCB1** (encoding P-glycoprotein), and **CYP3A5** (encoding cytochrome P450 3A5) were determined. Data from 15 healthy volunteers were used as controls.

**Results:** No statistically significant difference in systemic exposure of atorvastatin was observed between the 2 groups. However, patients with atorvastatin-related myopathy had 2.4-fold and 3.1-fold higher systemic exposures of the metabolites atorvastatin lactone (**P** < .01) and *p*-hydroxyatorvastatin (**P** < .01), respectively, compared with controls. There were no differences in frequencies of **SLCO1B1**, **MDR1**, and **CYP3A5** polymorphisms between the 2 groups.

**Conclusions:** This study disclosed a distinct difference in the pharmacokinetics of atorvastatin metabolites between patients with atorvastatin-related myopathy and healthy control subjects. These results are of importance in the further search for the mechanism of statin-induced myopathy. (Clin Pharmacol Ther 2006;79:532-9.)

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3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used in the prevention of cardiovascular events and are generally well tolerated. However, muscular side effects develop in some patients and may progress to potentially fatal rhabdomyolysis. The occurrence of myopathy is estimated to be 0.1% to 0.5% during statin monotherapy, whereas the incidence of rhabdomyolysis resulting in hospitalization has been estimated to be 0.44 per 10,000 patient-years for atorvastatin, simvastatin, and pravastatin.1,2 Cerivastatin was associated with an approximately 10-fold higher frequency of fatal rhabdomyolysis, which led to its withdrawal from the market in 2001.3,4

The reason myopathy develops in some patients as a result of treatment with statins is not understood. The increased frequency of rhabdomyolysis in combination with drugs interacting pharmacokinetically with statins...
suggests that the risk is associated with systemic statin exposure, but patient factors such as body size, age, sex, renal and hepatic function, hypothyroidism, diabetes, and debilitation might be of importance as well.1,4,5 The cellular mechanism of statin myotoxicity has been suggested to be directly linked to reduced mevalonic acid products in muscles, but this issue also contains many unanswered questions.5,6 One biochemical indication of statin-associated myotoxicity has been an increase in creatine kinase (CK) levels; however, reports on statin-associated myotoxicity without increase in CK have recently been presented.7,8

Worldwide, atorvastatin (atorvastatin acid) is the most frequently used statin. It is administered in the active lipid-lowering acid form and is interconverted to its corresponding lactone form in vivo (Fig 1).9 Both β-oxidation of the dihydroxy heptanoic acid side chain and glucuronidation of atorvastatin by uridine diphospho- (UDP)–glucuronosyltransferase 1A1 (UGT1A1) and UGT1A3 have been suggested to mediate interconversion from the acid to the lactone form of atorvastatin, and esterases (paraoxonases) appear to be responsible for hydrolysis of the lactone to the open acid form.10–12 The 2 hydroxylated metabolites mediated through cytochrome P450 3A (CYP3A) metabolism, o-hydroxyatorvastatin and p-hydroxyatorvastatin, are also present in both an active acid and a corresponding lactone form in vivo (Fig 1).13–15 It is mainly the lactone form of the drug that undergoes metabolism by CYP3A, because of a significantly higher affinity for CYP3A compared with that of the acid form.14 Atorvastatin has also been shown to be a substrate for the efflux transporter P-glycoprotein, as well as the organic anion transporting polypeptide OATP1B1.16–18 OATP1B1 has been indicated to be involved in hepatic uptake of atorvastatin, and P-glycoprotein limits the intestinal absorption and mediates the excretion of atorvastatin into bile.17,18

The aim of this study was to investigate whether the pharmacokinetics of either atorvastatin or its metabolites, or both, is altered in patients with atorvastatin-induced myopathy in the absence of interacting drugs and the possible link to polymorphism in genes relevant to the pharmacokinetics of atorvastatin.

METHODS

Subjects. Patients older than 18 years were recruited from the Lipid Clinic at the National Hospital in Norway where they had been referred because of problems with muscular side effects related to statin therapy. Diagnosis of muscular side effects from atorvastatin treatment was based on the patients’ subjective sense of severe muscular pain on treatment with atorvastatin,

![Chemical structure and metabolic pathways of atorvastatin and metabolites](image)
rapid improvement of muscular pain on withdrawal, and repeated symptoms on rechallenge with atorvastatin. Exclusion criteria were current treatment with drugs or herbal remedies with known pharmacokinetic interaction potential with atorvastatin, previous CK levels greater than 10 times the upper limit of normal range, pregnancy, and persistent muscular complaints after a 4-week washout period of statin treatment. Data from a recent study in which healthy volunteers were administered 10 mg atorvastatin for 1 week were used as controls.19 All participants in this study gave their written informed consent according to the Declaration of Helsinki. The study was recommended by The National Committees for Research Ethics and approved by the Norwegian Medicines Agency, Oslo, Norway.

**Study design.** Included patients who were receiving statin treatment underwent a 4-week washout period. After the washout period, 10 mg atorvastatin was administered daily for 1 week. The study subjects were instructed not to use drugs or dietary products with a known potential to affect the pharmacokinetics of atorvastatin during the study period. Data from a recent study in which healthy volunteers were administered 10 mg atorvastatin for 1 week were used as controls. All participants in this study gave their written informed consent according to the Declaration of Helsinki. The study was recommended by The National Committees for Research Ethics and approved by the Norwegian Medicines Agency, Oslo, Norway.

**Pharmacokinetic analysis.** The area under the plasma concentration versus time curve (AUC) was calculated by using the trapezoidal method in the dosing interval (0-24 hours) [AUC(0-24)]. Peak concentration ($C_{\text{max}}$) and time to $C_{\text{max}}$ ($T_{\text{max}}$) were determined from the actual measured values. The elimination half life ($t_{1/2}$) was...
estimated by linear regression analysis of the log-linear phase of the terminal plasma concentration curve.

Genotyping. Venous blood for genotyping was obtained from all subjects of the patient and control groups (all white). Deoxyribonucleic acid (DNA) was extracted with QIAamp (Qiagen, Valencia, Calif). Both groups were screened for relevant polymorphisms in MDR1 (G1199A, C1236T, G2677A/T, and C3435T), SLCO1B1 (*Ib [A388G, Asn130Asp], *4 [C463A, Pro155Thr], *5 [T521C, Val174Ala], and *I5 [haplotype consisting of *1b and *5]), and CYP3A5 (*2 [C27289A, Thr398Asn] and *3 [A6986G, splicing defect]). Mutations were determined by polymerase chain reaction–restriction fragment length polymorphism assays based on previously reported methods and nucleotide sequences of primers.21–24 The DNA fragment patterns generated after restriction enzyme digestion were analyzed by electrophoresis on a 3% agarose gel. Positive controls were kindly supplied by Dr D. Katz, Abbott Laboratories, Abbott Park, Ill (MDR1), Dr M. Nakajima, Division of Drug Metabolism, Kanazawa University, Kanazawa, Japan (SLCO1B1), and Dr R. van Schaik, Department of Clinical Chemistry, Erasmus MC, The Netherlands (CYP3A5).

Statistical analysis. A sample size of 5 subjects was needed to provide an 80% power of detecting a 100% difference in the AUC(0-24) of atorvastatin (α = .05). The SD was expected to be approximately 50% on the basis of previously published data.19 For Cmax the SD was expected to be approximately 75%, which required a sample size of 9 to evaluate a 100% difference in Cmax. A total of 14 patients were included to account for possible withdrawals. The Mann-Whitney test was used for statistical analysis, and P < .05 was considered to show statistical significance. StatView (Cary, NC) software was used for all statistical analysis.

RESULTS

Subjects. All 14 patients included in the study were given a diagnosis of atorvastatin-induced myopathy at the Lipid Clinic at the National Hospital in Norway between 0 and 48 months (median, 30 months) before inclusion in this study. One patient violated an inclusion criterion because of concurrent treatment with cyclosporine (INN, ciclosporin), a drug known to cause a substantial pharmacokinetic interaction with atorvastatin.19 This patient was therefore excluded from the data analysis. All of the remaining 13 patients reported either severe muscular pain or weakness, or both, during atorvastatin treatment, which rapidly improved on withdrawal of atorvastatin. Eleven of 13 patients underwent rechallenge with atorvastatin, during which symptoms of muscular side effects recurred in all 11 patients. In addition, 5 of the patients had CK elevations of more than 3 times the upper level of normal
With the exception of 1 patient (in whom atorvastatin-associated myopathy had recently been diagnosed), all patients had had muscular side effects with other statins as well. Three of the patients were receiving treatment for hypothyroidism, a known risk factor for statin-associated myopathy.5 Three of the subjects in the control group had muscular complaints during the 1-week treatment and were therefore not included in the current data analysis. Demographic data of patients and controls on inclusion are shown in Table I.

Pharmacokinetics. No significant difference in systemic exposure of atorvastatin was observed between the patient group and the control group (Fig 2, Table II). However, the AUC(0-24) of atorvastatin lactone was 2.4-fold higher ($P < .01$) and $C_{\text{max}}$ was 3.5-fold higher ($P < .01$) in the patient group compared with the controls (Table II). The terminal half-life of atorvastatin was significantly longer in patients versus controls (median, 15.8 hours; range, 7.1-65.0 hours and median, 6.9 hours; range, 5.1-10.9 hours, respectively ($P < .01$) (Table II). No statistically significant difference in terminal $t_{1/2}$ of atorvastatin lactone was observed.

Systemic exposure of the 2 hydroxyacid metabolites of atorvastatin was also significantly higher in patients compared with controls (Table II). The largest difference between the 2 groups was observed for $p$-hydroxyatorvastatin, which showed a 3.1-fold higher AUC(0-24) and a 5.0-fold higher $C_{\text{max}}$ in patients compared with controls ($P < .01$) (Fig 2, Table II).

Genotyping. Observed frequencies of polymorphisms in SLCO1B1, MDR1, and CYP3A5 for patients and controls are presented in Table III. In comparing the 95% confidence intervals for each group no statistical significant differences were found in polymorphism frequencies.

Clinical chemistry. There were no statistically significant differences in the changes in clinical chemistry parameters between the patients and the controls during the week of atorvastatin treatment (Table I). However, baseline CK, AST, ALT, total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were higher in the patient group than in the control group (Table I).

DISCUSSION

The main finding of our study is that patients with atorvastatin-related myopathy show an altered metabolic profile with significantly higher levels of atorvastatin lactone, $o$- and $p$-hydroxyatorvastatin, and no change in the parent compound compared with controls. The myotoxicity could therefore be related to either atorvastatin lactone or hydroxylated metabolites, or both. However, during concurrent treatment with atorvastatin and CYP3A4 inhibitors, which is associated with an increased risk of muscular side effects, the atorvastatin lactone level increases whereas hydroxylated metabolite levels decrease.4,13 Thus an increased level of lactone is a common feature of patients with atorvastatin-induced myotoxicity in the absence of interacting drugs and patients receiving concomitant treatment with CYP3A4 inhibitors.

Although atorvastatin lactone is inactive with respect to a lipid-lowering effect, it may still mediate muscular side effects, either through a direct toxic effect or through intracellular interconversion to the HMG-CoA reductase–inhibiting acid form. Atorvastatin lactone is about 1000-fold more lipophilic than the acid form on
the basis of estimated log D values at pH 7.4 (Advanced Chemistry Development/Chem Sketch, Toronto, Ontario, Canada), and is therefore expected to have a higher tissue penetration than the parent drug. Patients with increased levels of atorvastatin lactone, either inherently or as a result of CYP3A4 inhibition, could therefore be subjected to an increased tissue exposure, which might explain the increased risk of muscular side effects.

Because systemic exposure of atorvastatin was unchanged in the population with side effects, reduced elimination of atorvastatin lactone seems more likely than an increased formation of this metabolite. Renal function was not significantly different between the 2 groups, and the increased levels of atorvastatin lactone in the patient group probably reflect either diminished metabolism or excretion capacity, or both. The difference between the patient and the control groups observed in this study could not be explained by differences in polymorphism frequencies in the genes encoding CYP3A5, OATP1B1, or P-glycoprotein, all which have been suggested to be involved in atorvastatin disposition.14,16 The lack of association between genetic polymorphism in OATP1B1 and atorvastatin-induced myopathy was in contrast to a previous finding by Morimoto et al25 in a study in 10 Japanese patients. However, the lack of association observed in our study is not conclusive because of the restricted number of subjects. In addition, the increased exposure of both atorvastatin lactone and hydroxyacid metabolites could be a result of reduced capacity of alternative eliminating pathways not investigated in this study, such as CYP2C8, multidrug resistance protein 2 (MRP2), and UGT1A1 and 1A3.11,14,16,26,27 Decreased CYP3A4 activity in these patients is not likely because reduced, rather than increased, plasma levels of the CYP3A4-mediated hydroxyacid metabolites would have been expected.13

The several-fold increase in systemic exposure of atorvastatin lactone did not produce any significant change in plasma levels of atorvastatin. The only pharmacokinetic variable of atorvastatin that was signifi-

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**Fig 3.** Ratio of $p$-hydroxatorvastatin and atorvastatin 3 hours after the dose in patients with atorvastatin-induced myopathy and controls after a daily dosage of 10 mg atorvastatin for 1 week. Dotted line represents median.
significantly different between the 2 groups was the terminal half-life. Because the increased terminal half-life was not associated with an increased systemic exposure, the increase must be related to an increased volume of distribution rather than a reduced clearance. The relevance of this finding and the potential link to metabolite elevations are uncertain.

The control and the patient group differed in median age, lipid values, and CK, AST, and ALT levels (Table I). The difference in CK, AST, and ALT was probably caused by the patients’ previous use of statins and the fact that the 4-week washout period was too short to reach the true baseline. In addition, the frequency of use of other drugs was greater in the patient group compared with the control group, a difference that could possibly influence the baseline ALT and ALT values as well. However, the differences were not suspected to influence the pharmacokinetics of atorvastatin.

The need for an alternative or supplement to CK in the diagnosis of statin-induced myotoxicity has recently been proclaimed.30,31 The observed pharmacokinetic differences between the 2 groups in our study open a possible clinical use of metabolite/parent drug ratio as a potential new marker in the diagnosis and risk evaluation of atorvastatin-induced myopathy. The best resolution between the patient group and the control group in our study was observed for the ratio of p-hydroxyatorvastatin and atorvastatin 3 hours after the dose (Fig 3). For the ratio of atorvastatin lactone and atorvastatin the best resolution was obtained 5 hours after the dose, but this ratio gave a poorer separation between the groups compared with the ratio of p-hydroxyatorvastatin and atorvastatin. However, the choice of ratio and sampling time needs to be evaluated in larger prospective studies. It also remains uncertain whether the atypical metabolite profile in patients with atorvastatin-induced myopathy observed in this study is similar for other statins.

This is the first study to investigate whether the pharmacokinetics of either atorvastatin or its metabolites, or both, is altered in patients with atorvastatin-related myopathy. A distinct difference in the pharmacokinetics of atorvastatin metabolites between patients with atorvastatin-related myopathy and healthy controls was disclosed. These findings are important in the further search for the mechanism of statin-induced myopathy and may aid in understanding why some patients experience muscular side effects from statin therapy.

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We have no conflict of interest.

References
advisory on the use and safety of statins. Stroke 2002;33:2377-84.