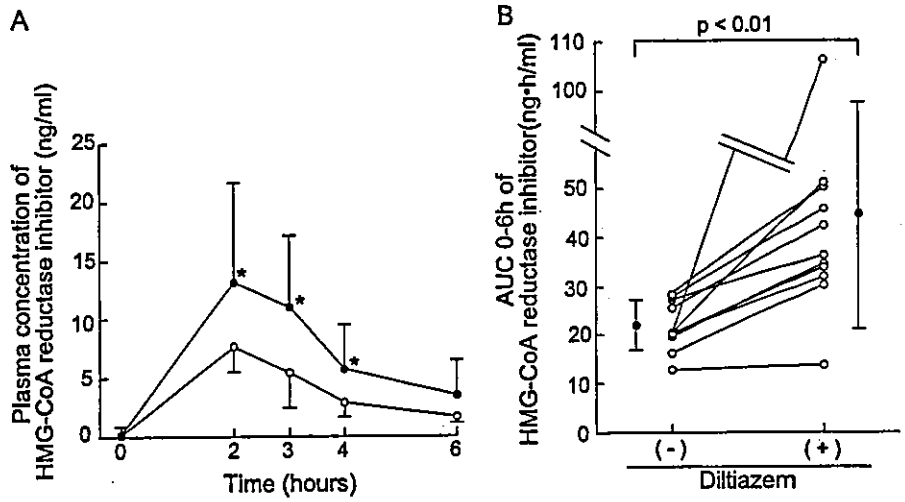

Fig. 1. Effect of diltiazem on plasma concentration and AUC_{0-6h} of HMG-CoA reductase inhibitor. (A) Plasma concentrations of HMG-CoA reductase inhibitor observed on the last day of 4 weeks of treatment with simvastatin (5mg/day) (open circles) or combined treatment with simvastatin (5mg/day) and diltiazem (90mg/day) (closed circles). Error bars represent S.D. *Significant difference from simvastatin monotherapy ($P < 0.05$). (B) Individual AUC_{0-6h} values for HMG-CoA reductase inhibitor (open circles) with (right) and without diltiazem (left) in the 11 patients. Closed circles with the bars indicate means ± S.D.

Tmax of diltiazem was not affected (3.1 ± 0.9 h) by simvastatin. Plasma diltiazem AUC_{0-6h} values were decreased by simvastatin in 9 of the 11 patients (Fig. 2B).

Pharmacodynamic interactions between simvastatin and diltiazem

Following 4 weeks of simvastatin monotherapy, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels were 206 ± 26 mg/dl, 129 ± 16 mg/dl, 50 ± 10 mg/dl, and 135 ± 73 mg/dl,

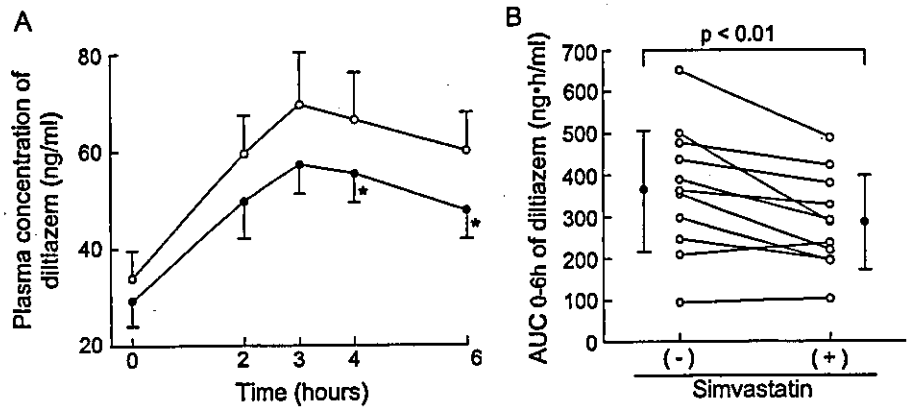

Fig. 2. Effect of simvastatin on plasma concentration and AUC_{0-6h} of diltiazem. (A) Plasma concentrations of diltiazem observed on the last day of 4 weeks of treatment with diltiazem (open circles) or combined treatment with simvastatin and diltiazem (closed circles). *Significant difference from diltiazem monotherapy ($P < 0.05$). (B) Individual AUC_{0-6h} values of diltiazem (open circles) with (right) and without simvastatin (left). Closed circles with the bars indicate means ± S.D.

respectively (Fig. 3A). These values were not different with those at the end of pretrial phase with simvastatin (5 mg/day) and enalapril (5 mg/day) (total cholesterol, 207 ± 23 mg/dl; LDL-cholesterol, 129 ± 15 mg/dl; HDL-cholesterol, 50 ± 10 mg/dl; triglyceride, 137 ± 68 mg/dl), suggesting that the treatment with simvastatin reached the plateau control during the pretrial phase. Co-administration of diltiazem and simvastatin further reduced the mean total and LDL-cholesterol levels to 196 ± 32 mg/dl ($P < 0.05$) (Fig. 3B) and 119 ± 17 mg/dl ($P < 0.05$), respectively, but did not influence HDL-cholesterol and triglyceride levels, which were 49 ± 11 mg/dl and 140 ± 72 mg/dl, respectively. On the other hand, after simvastatin was withdrawn during the last 4 weeks of diltiazem monotherapy, total cholesterol and LDL-cholesterol levels increased to 245 ± 33 mg/dl and 163 ± 21 mg/dl ($P < 0.01$), respectively, while HDL-cholesterol and triglyceride levels were not affected (51 ± 12 mg/dl and 157 ± 77 mg/dl, respectively).

After 4 weeks of simvastatin monotherapy, baseline systolic and diastolic BP increased from 142 ± 22 mm Hg to 152 ± 28 mm Hg ($P < 0.05$) and from 84 ± 12 mm Hg to 89 ± 10 mm Hg ($P < 0.05$), respectively, compared to baseline BP during the pre-trial phase with simvastatin and enalapril. Simvastatin did not exert any BP-lowering effect. Diltiazem decreased systolic BP from 146 ± 26 mm Hg to 124 ± 9 mm Hg and diastolic BP from 84 ± 11 mm Hg to 75 ± 6 mm Hg at 2 hours post-dose. This effect was not influenced by the combined treatment with simvastatin (baseline systolic BP, 138 ± 18 mm Hg; baseline diastolic BP, 83 ± 13 mm Hg; systolic BP at 2 hours post-dose, 129 ± 19; diastolic BP at 2 hours post-dose, 76 ± 12 mm Hg) (Fig. 4).

Serum aspartate aminotransferase (AST; normal range, 11–30 IU/l), alanine aminotransferase (ALT; normal range, 5–42 IU/l), lactate dehydrogenase (LDH; normal range, 115–208 IU/l) and creatine kinase (CK; normal range, 55–204 IU/l) levels appeared to increase, albeit without statistical significance, during the combined therapy period compared with those observed during the simvastatin monotherapy

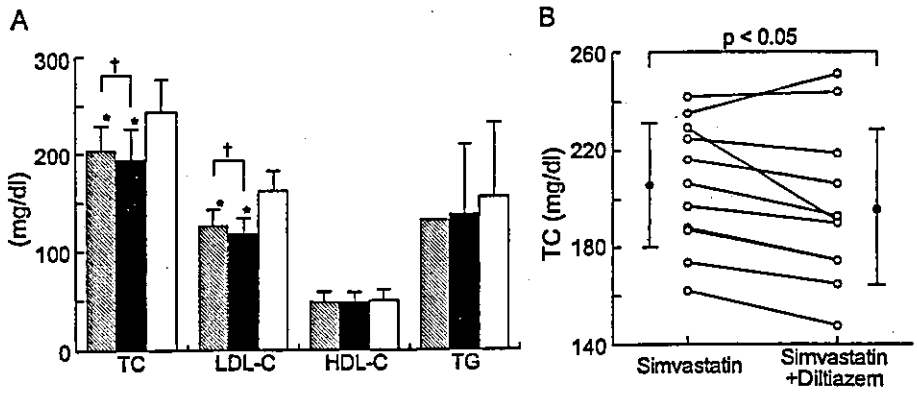

Fig. 3. Lipid profiles during simvastatin monotherapy, combined therapy with diltiazem and simvastatin, and diltiazem monotherapy. (A) Lipid profiles after 4 weeks of simvastatin monotherapy (5mg/day, hatched columns), combined treatment with simvastatin (5mg/day) and diltiazem (90mg/day) (closed columns) or diltiazem monotherapy (90mg/day, open columns). TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol and TG, triglyceride. * Significant difference from diltiazem monotherapy ($P < 0.05$). †Significant difference between simvastatin monotherapy and combined treatment with simvastatin and diltiazem ($P < 0.05$). (B) Total cholesterol levels in the 11 patients observed after 4 weeks of treatment with simvastatin (90mg/day) (left) or combined treatment with simvastatin (5mg/day) and diltiazem (90mg/day) (right). Closed circles with the bars indicate means ± S.D.

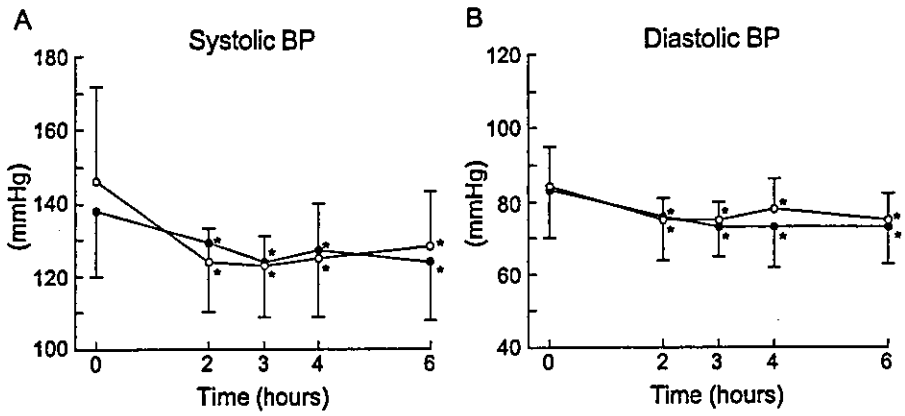

Fig. 4. Blood pressures during combined therapy with diltiazem and simvastatin, and diltiazem monotherapy. Systolic (A) and diastolic (B) BP before and 2, 3, 4 and 6 hours after an oral 30 mg dose of diltiazem with (closed circles) or without (open circles) simvastatin following 4 weeks of treatment with diltiazem alone (90mg/day) (open circles) or combined treatment with simvastatin (5mg/day) and diltiazem (90mg/day) (closed circles). * Significant difference from BP at 0 h ($P < 0.05$). Data are expressed as means ± S.D.

period: AST, 23.4 ± 4.3 IU/l vs. 21.3 ± 5.1 IU/l, ALT, 22.1 ± 5.6 IU/l vs. 18.9 ± 5.6 IU/l, LDH, 196 ± 42 IU/l vs. 187 ± 32 IU/l, and CK 142 ± 111 IU/l vs. 107 ± 45 IU/l, respectively.

Discussion

Simvastatin and diltiazem are often prescribed together for the treatment of hypercholesterolemia in patients with hypertension and/or angina pectoris (Gould et al., 1995; Gotto, 1998; Wood, 2001). In the Scandinavian Simvastatin Survival Study (4S) (1994), which demonstrated a reduction in nonfatal myocardial infarction, cardiovascular death, and total mortality by simvastatin treatment in patients with angina pectoris or previous myocardial infarction, more than 30% of the study population were treated with calcium antagonists including diltiazem. The efficacy and safety profiles of simvastatin and diltiazem are widely accepted (Chaffman and Brogden, 1985; The Scandinavian Simvastatin Survival Study, 1994; Hansson et al., 2000). The effect of diltiazem on the pharmacokinetics of simvastatin has been previously described, such that the Cmax and AUC of simvastatin after a single 20 mg oral dose of simvastatin increased by 3.6-fold and 5-fold, respectively, after 2 weeks of treatment with 120 mg diltiazem twice a day (Mousa et al., 2000). However, bi-directional pharmacokinetic interactions and the potential pharmacodynamic impact have not been prospectively studied.

Our prospective study demonstrates that long-term and low-dose co-administration of diltiazem and simvastatin results in two-fold increase of Cmax and AUC of HMG-CoA reductase inhibitor, which is accompanied by enhanced cholesterol-lowering effect of simvastatin in patients with hypercholesterolemia and hypertension. Interestingly, in contrast to the effect on the pharmacokinetics of simvastatin, the co-administration of simvastatin with diltiazem decreased the Cmax and AUC of diltiazem without affecting its BP-lowering effects.

These results are consistent with a retrospective study demonstrating that simvastatin caused a 33.3% cholesterol reduction in patients using diltiazem compared with 24.7% in those not using diltiazem (Yeo

et al., 1999). It has also been reported that doubling the dose of simvastatin further reduces serum cholesterol by an average of 5% (Roberts, 1997). This is compatible with our finding that a two-fold increase in the Cmax and AUC of HMG-CoA reductase inhibitor by co-administration of diltiazem with simvastatin was accompanied by a further 5% reduction in total cholesterol level. The results of our study suggest that patients who require both simvastatin and diltiazem may need a lower dose of simvastatin than when simvastatin is prescribed alone to achieve the desired reduction in total and LDL-cholesterol levels.

The mechanism underlying the decrease in the AUC of diltiazem by the combined therapy with simvastatin remains unknown. Diltiazem is extensively metabolized in the liver into its host metabolites, primarily by deacetylation and demethylation by CYP3A4 in vitro and in vivo (Chaffman and Brogden, 1985; Pichard et al., 1990; Sutton et al., 1997; Jones et al., 1999; Nakagawa and Ishizaki, 2000; Yeo and Yeo, 2001; Kosuge et al., 2001), and probably in part by CYP2C8/9 (Sutton et al., 1997). In addition, diltiazem has been shown to increase the metabolic ratio of debrisoquine (Sakai et al., 1991), suggesting a possible interference with CYP2D6 (Molden et al., 2002). It is possible that the relevant enzyme activity to metabolize diltiazem or its metabolite(s) might be induced by themselves. Alternatively, simvastatin and/or its metabolite(s) might enhance the activity of enzyme(s) involved in the metabolism of diltiazem after the long term coadministration. Although the Cmax and AUC of diltiazem were decreased by simvastatin, blood pressure-lowering effect of diltiazem was not influenced by simvastatin. Heart rate of the patients during combined treatment with simvastatin did not differ from that during the diltiazem monotherapy period: 70 ± 10 beats/min vs. 68 ± 7 beats/min, respectively. It is likely that the pharmacokinetic interaction such as the 21% reduction in both the Cmax and AUC of diltiazem was not sufficient to alter pharmacodynamic response. However, we cannot exclude the possibility that the power was not enough to detect the pharmacodynamic differences. Further investigation is required to clarify the pharmacodynamic impact on blood pressure and the mechanism responsible for the changes in the pharmacokinetic behavior of diltiazem by the combined treatment with simvastatin.

The combined therapy increased the AUC of HMG-CoA reductase inhibitor by as much as 422% in one patient and as little as 7 % in another, suggesting a considerable inter-individual variability in the effect of diltiazem on the levels of HMG-CoA reductase inhibitor (Fig. 1B). However, this pharmacokinetic variation did not account for the differences in the pharmacodynamic responses to simvastatin (correlation coefficient: $r = 0.106$, not significant) (Fig. 5A). On the other hand, there was a significant correlation between the AUC of diltiazem and the AUC of HMG-CoA reductase inhibitor ($r = 0.73$, $P < 0.05$) (Fig. 5B). For example, one patient showing the lowest value of the AUC of diltiazem showed the lowest value for the AUC of HMG-CoA reductase inhibitor, suggesting that this patient might be an individual with a high CYP3A4 activity. These findings taken together strongly suggest that simvastatin and diltiazem could be metabolized, at least in part, through a common or shared pathway.

Simvastatin is generally well tolerated and causes few subjective side-effects during chronic treatment, however, rhabdomyolysis is a rare side effect of this HMG-CoA reductase inhibitor that appears to be dose-related. The doses of simvastatin (5 mg/day) and diltiazem (90 mg/day) used in this study are lower than those recommended in Western countries, because these doses are common and approved in the Japanese formulary and have been shown to be sufficient to treat Japanese patients at the clinical practice (Matsuzaki et al., 2002). It is noteworthy that the pharmacokinetic and pharmacodynamic interactions take place even at the lower doses. Furthermore, the levels of AST, ALT, LDH and CK appeared to increase during the combined therapy with simvastatin and diltiazem compared to the

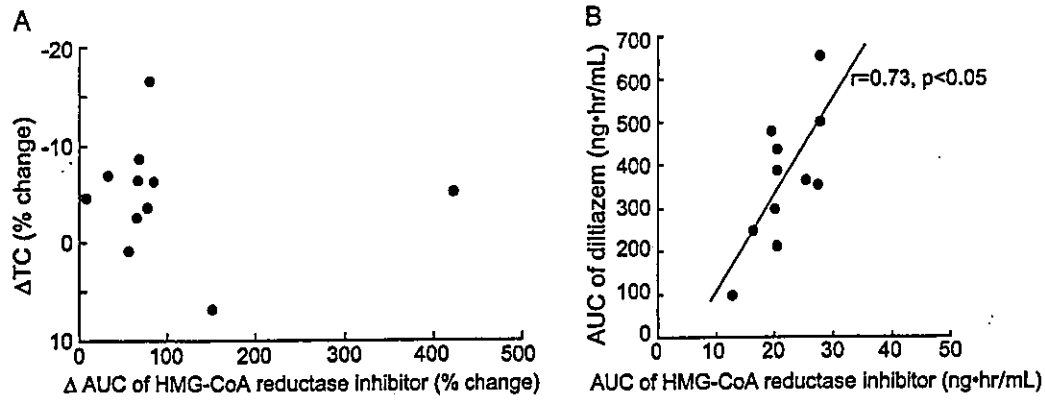

Fig. 5. (A) Percent changes in plasma concentration of HMG-CoA reductase inhibitor versus plasma total cholesterol (TC) concentration after the combined treatment with simvastatin and diltiazem in the 11 patients. Correlation coefficient was 0.106 (not significant). (B) Relationship between the AUCs of HMG-CoA reductase inhibitor and diltiazem in the 11 patients during monotherapy ($r = 0.73$, $P < 0.05$).

simvastatin mono-therapy. The findings strongly suggest that careful monitoring should be carried out for patients under combined treatment with simvastatin and diltiazem at higher doses to avoid any increase in risk of serious adverse effects.

Conclusion

This study is the first to show the bi-directional pharmacokinetic and pharmacodynamic interactions between diltiazem and simvastatin after long-term treatment with both drugs. Combined treatment with diltiazem and simvastatin increases the Cmax and AUC of HMG-CoA reductase inhibitor and further reduces total and LDL-cholesterol levels. On the other hand, the combination decreases the Cmax and AUC of diltiazem without affecting its blood pressure-lowering effect. These interactions should therefore be taken into consideration, and pharmacokinetic and pharmacodynamic monitoring may be necessary when these drugs are used concomitantly.

Acknowledgments

The authors are grateful to Dr. Quang-Kim Tran (University of Missouri-Kansas City) for his helpful insights and to H. Kobayashi for technical assistance.

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Original Article

Interaction between Amlodipine and Simvastatin in Patients with Hypercholesterolemia and Hypertension

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3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are often prescribed in association with antihypertensive agents, including calcium antagonists. Simvastatin is an HMG-CoA reductase inhibitor that is metabolized by the cytochrome P450 (CYP) 3A4. The calcium antagonist amlodipine is also metabolized by CYP3A4. The purpose of this study was to investigate drug interactions between amlodipine and simvastatin. Eight patients with hypercholesterolemia and hypertension were enrolled. They were given 4 weeks of oral simvastatin (5 mg/day), followed by 4 weeks of oral amlodipine (5 mg/day) co-administered with simvastatin (5 mg/day). Combined treatment with simvastatin and amlodipine increased the peak concentration (C_{max}) of HMG-CoA reductase inhibitors from 9.6±3.7 ng/ml to 13.7±4.7 ng/ml ($p<0.05$) and the area under the concentration-time curve (AUC) from 34.3±16.5 ng h/ml to 43.9±16.6 ng h/ml ($p<0.05$) without affecting the cholesterol-lowering effect of simvastatin. This study is the first to determine prospectively the pharmacokinetic and pharmacodynamic interaction between amlodipine and simvastatin. (*Hypertens Res* 2005; 28: 223–227)

Key Words: **drug interaction, simvastatin, amlodipine, hypercholesterolemia**

Introduction

Control of hypercholesterolemia is important for the prevention of coronary artery disease (CAD) (*1–5*). Currently, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are the first-choice therapeutic agents for patients with hypercholesterolemia (*6–8*). The HMG-CoA reductase inhibitor simvastatin is widely used and has been shown to reduce morbidity and mortality from CAD (*9*). Simvastatin is an inactive lactone pro-drug that is hydrolyzed by esterases to simvastatin acid, the active competitive inhibitor of HMG-CoA reductase (*10–12*). Simvastatin and simvastatin acid are mainly metabolized by the cytochrome P450 (CYP) 3A4 to 3′,5′-dihydrodiol, 3′-hydroxy and 6′-exomethylene (*10–12*). The pharmacokinetics of simvastatin has been reported to be affected by potent CYP3A4 inhibitors such as itraconazole (*13*), erythromycin (*14*), verapamil (*14*) and nelfinavir (*15*). Moreover, we have previously reported that diltiazem, which is a selective inhibitor of CYP3A4 (*16, 17*), caused a 2-fold increase of the area under the concentration-time curve (AUC) of HMG-CoA reductase inhibitors (*18*).

Hypercholesterolemia is often accompanied by hypertension, an associated risk factor for CAD (*19–21*). Calcium antagonists have been widely used in the treatment of hypertension and/or angina pectoris (*22–26*), and are often prescribed in association with a lipid-lowering agent such as simvastatin. Amlodipine is one of the 1,4-dihydropyridine calcium antagonists with a long elimination half-life (*27–29*). Amlodipine undergoes the oxidative metabolism of dihydro-

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Table 1. Patient Demographics and Basic Medical Data

Age (years old)	64.1±6.0
Sex (male/female)	5/3
Body weight (kg)	61.5±5.9
Total cholesterol (mg/dl)	253±31
LDL-cholesterol (mg/dl)	164±26
HDL-cholesterol (mg/dl)	54±9
Triglyceride (mg/dl)	179±95

Values are mean±SD. LDL, low-density lipoprotein; HDL, high-density lipoprotein.

pyridine to a pyridine analogue by CYP3A4 (*30*). In an *in-vitro* study, amlodipine was shown to have strong inhibitory effects on CYP1A1, CYP2B6 and CYP2C9, and a weak inhibitory effect on CYP3A4 when using microsomes from human B-lymphoblast cells expressing CYP (*31*). Although amlodipine is one of the most frequently used calcium antagonists, the drug interaction between amlodipine and substrate drugs for CYP3A4 has not been clinically investigated. In this study we prospectively studied the pharmacokinetic and pharmacodynamic drug interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension.

Methods

Subjects

Eight patients with mild hypertension and hypercholesterolemia who had been treated with simvastatin (5 mg/day) and the angiotensin-converting enzyme inhibitor enalapril (5 mg/day) for more than 3 months were enrolled. Before the start of any antihypertensive therapy, the mean systolic and diastolic blood pressure levels (SBP/DBP) were 151±29 mmHg and 88±11 mmHg, respectively. The patient demographics and basic medical data are shown in Table 1. Patients had no history of hepatic or renal disease. The study protocol was approved by the Ethical Committee of Hamamatsu University School of Medicine. All subjects gave written informed consent before participating in the study.

Study Design

This was a two-phase fixed-order design study. In the first period, patients were administered oral simvastatin (5 mg/day) alone for 4 weeks. In the second period, patients were co-administered amlodipine (5 mg/day) and simvastatin (5 mg/day) for 4 weeks. No drug other than simvastatin and amlodipine was taken during the study period.

Blood Sampling

Blood samples were obtained on the last day of each of the trial periods. After an overnight fast, a pre-dosing venous blood sample was taken, which was used to measure serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) enzymatically, and the low-density lipoprotein cholesterol (LDL-C) concentration was calculated according to the Friedewald formula method (*32*). All patients drank a glass of water after swallowing the tablets. Blood samples were then taken 2, 3, 4 and 6 h after simvastatin administration. A standardized breakfast and lunch were served 2 and 4 h after drug intake. Plasma was separated within 30 min and stored at −70°C until analysis.

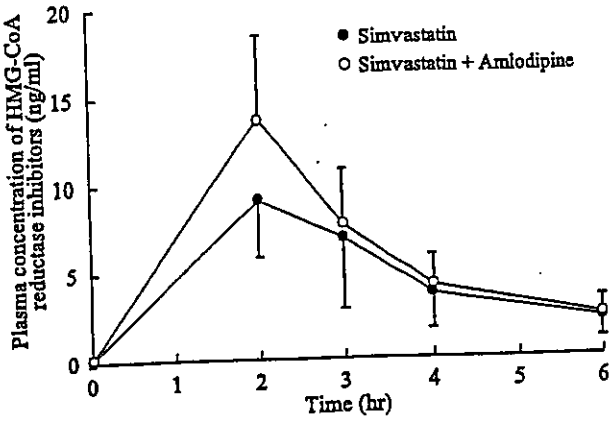

Fig. 1. *Time profiles of the mean plasma concentrations of HMG-CoA reductase inhibitors on the last day of 4 weeks of treatment with simvastatin (5 mg/day) or combined treatment with simvastatin (5 mg/day) and amlodipine (5 mg/day). Each point represents the mean±SD.*

Determination of Simvastatin HMG-CoA Reductase Inhibitor Concentrations

Plasma concentrations of HMG-CoA reductase inhibitors were determined as previously described (*33*). An equal volume of methanol was added to the plasma samples and the mixtures were vortexed thoroughly, kept on ice for 10 min, and centrifuged. Fifty microliters of the supernatants were dried in an evaporator (SpeedVac; Savant Instruments, Farmingdale, USA). The reaction mixture (96 µl) was added directly to the dried residues to make a final volume of 100 µl containing 0.1 mol/l KPO_4 (pH 7.4), 10 mmol/l 1,4-dithiothreitol (DTT), 0.2 mmol/l $NADH^+$ (made fresh daily), 5 mmol/l glucose-6-phosphate, 1.4 U/ml glucose-6-phosphate dehydrogenase and 1 mg/ml bovine serum albumin. The reaction mixture was incubated for 5 min at 37°C, and soluble rat liver HMG-CoA reductase was added to 2 µl buffer A: 0.04 mol/l KPO_4 (pH 7.4), 0.05 mol/l KCl, 0.1 mol/l sucrose, 0.03 mol/l ethylenediaminetetraacetic acid (EDTA) and 0.01 mol/l DTT (added immediately before use). The mixture was incubated at 37°C for 5 min in the presence of the inhibitor-con-

Table 2. Pharmacokinetic Parameters of Simvastatin HMG-CoA Reductase Inhibitor Concentrations

	C_{max} (ng/ml)	$t_{1/2}$ (h)	AUC(0–∞) (ng h/ml)
Simvastatin	9.6±3.7	2.08±0.59	34.3±16.5
Simvastatin+amlodipine	13.7±4.7*	1.97±0.61	43.9±16.6*

Values are mean±SD. C_{max}, maximal measured concentration; $t_{1/2}$, the elimination half-life; AUC(0–∞), area under the concentration-time curve. *$p<0.05$ *vs.* simvastatin monotherapy.

taining plasma sample. The reaction was started with 2 µl of 1.25 mg/ml HMG-CoA containing 17.5 µCi/ml glutaryl-3-[^{14}C]HMG-CoA. After an additional 6-min incubation at 37°C, 20 µl of 5 mol/l HCl was added to lactonize the mevalonic acid formed. After 15 min, 3.5 ml of a 1:1 suspension of BioRad AG 1 × 8 resin (200–400 mesh) was added and the tubes (13 × 100) were thoroughly vortexed. [^{14}C]Mevalonolactone was filtered from the resin suspension through polystyrene filters (pore size 70 µm; EverGreen, Los Angeles, USA) into scintillation vials containing 15 ml of Aquasol-2 (New England Nuclear, Newton, USA) and counted on a scintillation counter. The percentage of inhibition was converted to the inhibitor concentration using a standard curve constructed by extracting from the control plasma containing known amounts of L-654, 969, the free acid form of simvastatin. The results were expressed as nanograms of inhibitor per milliliter of plasma. The intra- and inter-day coefficients of variation for the HMG-CoA reductase activity assay were less than 6%.

Data Analysis

The pharmacokinetics of simvastatin was characterized by the peak concentration (C_{max}), the time to C_{max} (T_{max}), the elimination half-life ($t_{1/2}$) and the area under the plasma concentration-time curve from 0 to infinity [AUC(0–∞)]. The C_{max} and T_{max} were obtained directly from the original data. The terminal rate constant (k_e) used for the extrapolation was determined by regression analysis of the log-linear part of the concentration-time curve for each subject. The $t_{1/2}$ was determined by $0.693/k_e$. The AUC(0–∞) was calculated by the trapezoidal rule for the observed values and subsequent extrapolation to infinity. Data are represented as the mean±SD. Data were analyzed by a paired *t*-test or Wilcoxon signed-rank test where appropriate. Differences with p values <0.05 were considered statistically significant.

Results

No subjects reported a serious clinical, laboratory or other adverse effect, and no subjects were discontinued.

Pharmacokinetics of Simvastatin HMG-CoA Reductase Inhibitor Concentrations

Plasma concentrations of HMG-CoA reductase inhibitors after oral simvastatin dosing with or without amlodipine are shown in Fig. 1, and pharmacokinetic parameters of simvastatin are shown in Table 2. Co-administration of amlodipine with simvastatin significantly increased the C_{max} and AUC(0–∞) of HMG-CoA reductase inhibitors to 1.4- and 1.3-fold, respectively, in simvastatin monotherapy, but did not affect the $t_{1/2}$ and T_{max} of HMG-CoA reductase inhibitors.

Pharmacodynamics

Lipid profile, including TC, LDL-C, HDL-C, and TG during simvastatin monotherapy and combined treatment with simvastatin and amlodipine, are shown in Fig. 2. There were no significant differences in lipid profiles between the two periods.

The SBP and DBP values are shown in Table 3. Both measures were significantly higher during simvastatin monotherapy than during the pretrial control period with enalapril. After administration of amlodipine, both SBP and DBP tended to decline ($p=0.06$ and $p=0.08$, respectively). The blood pressure values during combined treatment with simvastatin and amlodipine did not differ from those during the pretrial control period with enalapril.

Discussion

Calcium antagonists and HMG-CoA reductase inhibitors are often prescribed together for the treatment of hypertension and/or angina pectoris in patients with hypercholesterolemia (*1*, *6*, *7*). Amlodipine is used with many drugs, such as oral hypoglycemic drugs, β-blockers, angiotensin-converting enzyme inhibitors, and so on. However, there have been no reports on the interaction between amlodipine and any other drug, with the exception that the interaction of amlodipine with grapefruit juice was shown to increase the AUC of amlodipine (*34*). This study is the first to report that amlodipine affected the plasma concentrations of HMG-CoA reductase inhibitors.

Simvastatin is hydrolyzed by esterases to simvastatin acid, which is an active inhibitor of HMG-CoA reductase (*10–12*). Simvastatin is extensively metabolized to several oxidative products by CYP3A4 (*10–12*). Some of the hydroxyl acid forms of these products also inhibit HMG-CoA reductase (*10*, *11*). In this study, we measured the total HMG-CoA reductase inhibitory activity resulting from simvastatin acid and all other active acid metabolites of simvastatin, since this level is

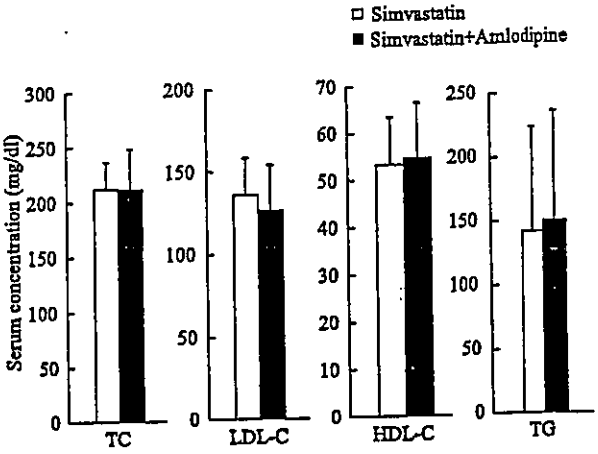

Fig. 2. *Mean levels of serum lipid parameters on the last day of 4 weeks of treatment with simvastatin (5 mg/day) or combined treatment with simvastatin (5 mg/day) and amlodipine (5 mg/day). TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides. Each column represents the mean±SD.*

believed to be relevant to the systemic adverse effects for this class of agents (*35*).

The pharmacokinetics of simvastatin has been shown to be affected by potent CYP3A4 inhibitors (*13–15, 18*). Amlodipine, which is metabolized by CYP3A4, has been reported to show inhibitory effects on CYP3A4 *in vitro* (*31*). However, the influence of amlodipine on the substrate drugs of CYP3A4 has not been clarified yet. In this study, amlodipine significantly increases the AUC of HMG-CoA reductase inhibitors after co-administration of simvastatin by 30%. It has been reported that the AUC of HMG-CoA reductase inhibitors was increased 4-fold with itraconazole (*13*), which is known to be a potent inhibitor of CYP3A4. Some studies have show adverse effects, including rhabdomyolysis, in patients treated with simvastatin and CYP3A4 inhibitors such as itraconazole and ketoconazole (*8*). These reports suggested that the co-administration of simvastatin with these inhibitors enhanced the risk of adverse effects, because of the dose-dependent toxicity of HMG-CoA reductase inhibitors. In our previous study, diltiazem increased the AUC of HMG-CoA reductase inhibitors 2-fold (*18*). On the other hand, amlodipine increased the AUC of HMG-CoA reductase inhibitors by only 30% in this study. In addition, it has been reported that the CYP3A4 inhibitory effect of diltiazem was higher than that of amlodipine after therapeutic doses (*36*). Therefore, the difference of the impact on the plasma concentrations of HMG-CoA reductase inhibitors may depend on the difference of the CYP3A4 inhibitory potency between amlodipine and diltiazem.

It has been reported that an increase in the plasma concentrations of HMG-CoA reductase inhibitors following co-

Table 3. Systolic BP and Diastolic BP during Pretrial Control Period with Enalapril, Simvastatin Monotherapy and Combined Treatment with Simvastatin and Amlodipine

	Systolic BP (mmHg)	Diastolic BP (mmHg)
Simvastatin+enalapril (pretrial control period)	135±19	78±13
Simvastatin	152±22*	89±13*
Simvastatin+amlodipine	140±17	81±11

Values are mean±SD. BP, blood pressure. *$p<0.05$ *vs.* simvastatin+enalapril.

administration of simvastatin and diltiazem resulted in a reduction of TC and LDL-C levels (*18*). However, we did not observe such a reduction of TC and LDL-C levels, despite the fact that amlodipine increased the plasma concentrations of HMG-CoA reductase inhibitors. The pharmacokinetic interactions observed in the present study, such as the 30% increase in the AUC of HMG-CoA reductase inhibitors, may not have been sufficient to alter the pharmacodynamic response. Moreover, we cannot exclude the possibility that the number of patients was not sufficient to detect the pharmacodynamic differences. Further investigations will be needed to clarify the pharmacodynamic impact of simvastatin with amlodipine on TC and LDL-C.

In conclusion, this study is the first report of the drug interaction between simvastatin and amlodipine after a long-term treatment. Although amlodipine increases the plasma concentrations of HMG-CoA reductase inhibitors, the impact of amlodipine on simvastatin is smaller than that of diltiazem. Since these drugs are often used concomitantly for patients with hypertension and hypercholesterolemia, amlodipine could be used more safely with simvastatin than diltiazem.

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HMG-CoA 還元酵素阻害薬 Pravastatin 服用患者におけるリスクファクターと血清脂質値に関する調査

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Risk Factors and Serum Cholesterol Concentrations in the Patients Given HMG-CoA Reductase Inhibitor, Pravastatin

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Purpose : HMG-CoA reductase inhibitors (statins) have been widely used in the treatment of hypercholesteremia in Japan as well as in Western countries. Although statins have been shown to be effective in the prevention of coronary heart disease (CHD) in high-risk patients, the potential benefit of statins on the overall mortality has not been proven in subjects at lower risk for CHD. In this study, we investigated the risk factors and serum cholesterol concentrations in patients given pravastatin.

Methods : Patients who were given pravastatin during the period from June 2002 until May 2003 in the Hamamatsu University Hospital were studied. Data for height, body weight, age, gender, smoking and history of diabetes mellitus, hypertension and CHD in the patients were collected from their case records. Serum cholesterol concentrations were determined before and after the treatment with pravastatin. The ethics committee in the Hamamatsu University approved this study.

Results : There were 213 male (37.4%) and 356 female (62.6%) patients given pravastatin. The mean age of the patients was 63.9 yrs, and % of the patients aged under 50 yrs was 10.7%. Seventy-seven % of the patients had no history of CHD. Female patients without smoking, diabetes mellitus, hypertension and CHD constituted 17% of all patients. Total and LDL cholesterol levels in all groups were significantly decreased by 17.6% and 25.5%, respectively, after the administration of pravastatin. Treatment with pravastatin was started at the lower total cholesterol levels in male patients or patients with CHD than in female patients or patients without CHD.

Conclusion : Our results suggest that significant numbers of patients with a low risk for CHD were prescribed the statins, and that placebo-controlled large-scale trials should be conducted to demonstrate the benefit and safety of statin treatment on overall mortality in Japan.

Key words : HMG-CoA reductase inhibitors, statins, pravastatin, hypercholesteremia, risk factor

緒　論

近年，わが国においてもライフスタイルの欧米化などにより動脈硬化性疾患が増加し，死因統計で癌と並ぶ大きな位置を占めるようになった．国内外の多くの研究から血清コレステロール値が上昇するに従い，男

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Table 1 Demographic characteristics of the patients treated with pravastatin at the point of the survey

	Male	Female	Total
Number of patients	213 (37.4%)	356 (62.6%)	569 (100%)
Age [years]	63.2±11.6	64.2±12.2	63.9±12.0
Height [cm]	164.3±6.2	151.8±6.1	156.5±6.1
Weight [kg]	63.2±10.0	52.0±8.9	56.2±9.3
Periods for the treatment with pravastatin [month]	48.9±40.4	59.5±46.5	55.5±44.6
Smoking	63 (11.1%)	31 (5.4%)	94 (16.5%)
Risk factors			
Coronary heart disease	80 (14.1%)	52 (9.1%)	132 (23.2%)
Diabetes mellitus	73 (12.8%)	126 (22.1%)	199 (34.9%)
Hypertension	141 (24.8%)	206 (36.2%)	347 (61.0%)

Values are numbers of patients (% of all patients (n=569)), or mean ± SD.

女を問わず虚血性心疾患発症リスクは増加することが示され[1-3]，高コレステロール血症治療の重要性がますます高まっている．高コレステロール血症に対する薬物療法の選択肢はいくつかあるが，なかでも3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) 還元酵素阻害薬（スタチン）は強力なLDLコレステロール (LDL-C) 低下作用を有することから，現在第一選択薬として用いられている．欧米諸国を中心に行われた多くの大規模臨床試験では，虚血性心疾患患者を対象とした二次予防試験だけでなく，虚血性心疾患既往歴のない一次予防の場合においても，スタチンによるLDL-Cの低下が心血管イベントの発生率や虚血性心疾患死亡率，さらに総死亡率を低下させることが示されている[4-6]．

一方，わが国では虚血性心疾患の発生率が欧米諸国の1/4から1/10と低いことが知られている[7]．さらに遺伝的素因やライフスタイルも欧米諸国のそれらと異なることから，欧米諸国における大規模試験の結果を日本人にそのまま適応できるかどうか疑問視する意見もある[8]．

わが国においては1989年にpravastatinが発売されて以来，数種のスタチンが臨床適用され，多くの患者に投与されている．しかしわが国においてスタチンがどのような背景を持つ患者に使用されているかを実態調査した報告はほとんどない．スタチンの適正使用を推進するためにも，スタチン使用の実態を把握することは重要である．本研究では，浜松医科大学附属病院においてpravastatinを投与されている患者を対象とし，リスクファクター（年齢，性，喫煙習慣，糖尿病，高血圧，虚血性心疾患の既往）およびpravastatin服用前後の血清脂質値を調査した．

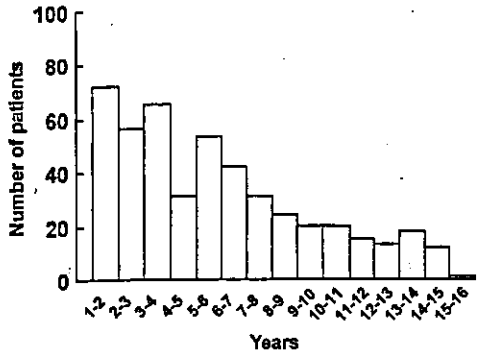

Fig. 1 Periods treated with pravastatin

方　法

浜松医科大学附属病院において2002年6月から2003年5月の間にpravastatin（メバロチン®）を投与された全患者(581例)中，カルテおよび病院オーダリングシステムを調査しえた569例を対象とした．調査期間（2003年6月～2003年8月）中のpravastatin最終投与日における対象患者の身長，体重，年齢と喫煙歴ならびに虚血性心疾患，糖尿病および高血圧の既往の有無について調査した．さらにpravastatin服用前と調査時における血清脂質値が調査可能であった478例において総コレステロール (TC)，HDLコレステロール (HDL-C)，LDLコレステロール (LDL-C) およびトリグリセリド (TG) を調査した．Pravastatin服用前かつ調査時の臨床検査値をカルテないしオーダリングシステム上から調査することが可能であった症例においては，アスパラギンアミノトランスフェラーゼ (AST)，アラニンアミノトランスフェラーゼ (ALT)，クレアチンキナーゼ (CK)，血清クレアチニン (s-Cre)，血液尿素窒素 (BUN)，随時血

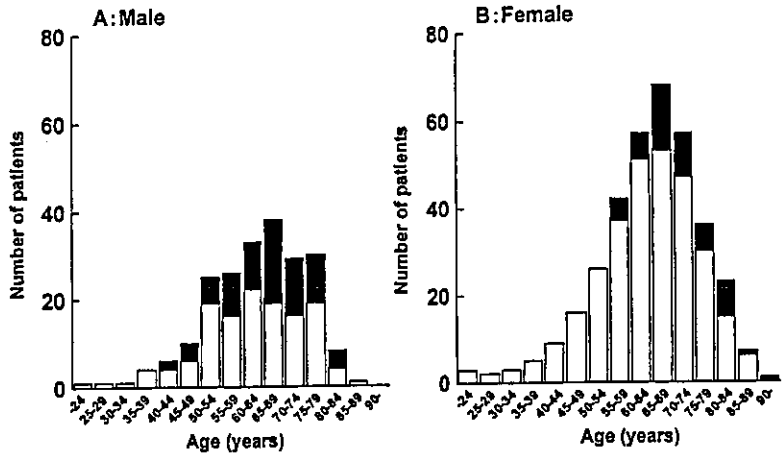

Fig. 2 Number of male (A) and female (B) patients with coronary heart disease (CHD, ■) or without CHD (□)

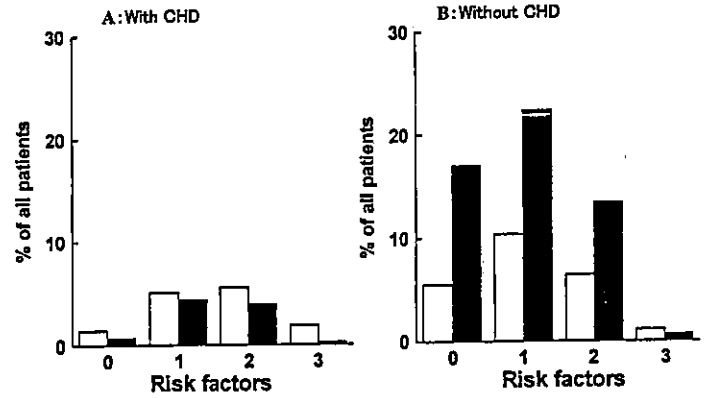

Fig. 3 Number of risk factors (smoking, diabetes mellitus and hypertension) in the patients with (A) and without (B) coronary heart disease (CHD)

Data are % of all patients (n=569).
□: Male, ■: Female

糖 (BS) およびヘモグロビン A_{1c} (HbA_{1c}) についても調査した．データは平均値±標準偏差で表示した．統計学的解析は Student's t-test を用い，危険率5%未満を有意差ありと判定した．本研究は浜松医科大学倫理委員会の承認の下に施行した．

成　績

調査した患者のうち男性は213例 (37.4%)，女性は356例 (62.6%) であり，女性患者が男性患者の1.7倍を占めた．対象患者の年齢は63.9±12.0歳であり男女間に有意な差異は認められなかった (Table 1)．対象患者における pravastatin 服用期間は1年以内の頻度が最も高く経時的に減少する傾向が認められた (Fig. 1)．また平均服用期間は55.5±44.6月であった．対象患者の既往歴では高血圧が最も多く全体の61.0%であった．次いで糖尿病が34.9%，虚血性心疾患が23.2%，喫煙が16.5%であった (Table 1)．対象患者の年齢分布では男女ともに65歳から69歳にピークが認められ，49歳以下の患者は全体の10.7%であった．虚血性心疾患の既往のある患者は男性では40歳から認められたのに対し，女性では55歳からであった (Fig. 2)．

虚血性心疾患の既往の有無について調べたところ，男性患者の37.6% (全体の14.1%) と女性患者の14.6% (全体の9.1%) では虚血性心疾患の既往を有していた．すなわち全対象患者の23.2%が二次予防目的のスタチン使用であった (Table 1)．一方，全対象患者のうち22%においては，虚血性心疾患の既往がなく，かつ喫煙歴，糖尿病，高血圧のいずれも有していなかった．その中で女性患者は97例 (17.1%) を占めた (Fig. 3)．

Pravastatin 服用開始前後における血清脂質値の調

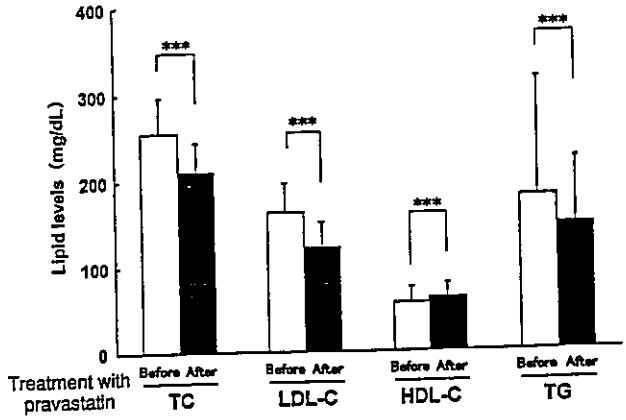

Fig. 4 Lipid profiles in the patients before (□) and after (■) the treatment with pravastatin
TC : Total cholesterol, LDL-C : LDL cholesterol, HDL-C : HDL cholesterol, TG : triglyceride, ***$p<0.001$

査によると，対象患者の TC は 255±41 mg/dL から 210±34 mg/dL へと 17.6%有意に低下した．同様に LDL-C および TG はそれぞれ 25.5%および 18.7%有意に減少した．一方 HDL-C は 8.7%有意に増加した (Fig. 4)．さらに対象患者を性別および虚血性心疾患の既往によって層別化したところ，TC，LDL-C および TG は性別および虚血性心疾患の既往にかかわらずいずれの群においても有意に低下した (Fig. 5)．また HDL-C は女性で心血管疾患の既往がある群を除き有意に増加した．さらに男女ともに虚血性心疾患の既往がある群では既往なし群に比べ，また虚血性心疾患の既往にかかわらず，女性に比べ男性においてより低い TC レベルから pravastatin の投与が開始されていた (Fig. 5 A)．

Table 2 に pravastatin 服用患者における服用開始前および服用後の臨床検査値を，糖尿病既往あり群となし群に分けて示した．糖尿病既往なし群では，いずれの検査値においても服用前後で有意な差は認められなかった．一方，糖尿病既往あり群では pravastatin 服用後では，BUN および s-Cre は有意に高値を，HbA_{1c} は有意に低値を示した．

考　察

本研究では，わが国においてスタチンがどのような背景を持つ患者に使用されているかを推測する目的で，浜松医科大学附属病院において pravastatin を投与されている患者の背景を調査し，さらに本薬剤が血清脂質値に及ぼす影響について検討した．

今回は pravastatin 服用患者の 569 症例の背景について調査した．この症例数は浜松医科大学附属病院における pravastatin 処方数の 98%にあたる．今回の対象患者において虚血性心疾患既往歴のある患者は全体の 23%のみであった．現在までに行われている大規模臨床試験から，虚血性心疾患の二次予防におけるスタチン投与の有用性は明確に示されているが，一次予防の場合には二次予防の場合に比べその有用性が低くなることが知られている[4]．今回の調査から，わが国におけるスタチン投与患者の多くが，比較的有用性の低いと考えられる一次予防であると推察された．また女性で虚血性心疾患，糖尿病，高血圧の既往および喫煙歴のない患者が全体の 17%占めていた．虚血性心疾患に対するスタチン投与の有用性は，患者のベースラインリスクに依存することが明らかにされており[9]，虚血性心疾患の絶対リスクが欧米諸国に比べ低いわが国において一次予防，とくに高コレステロール血症のみを有する女性患者など，低リスク群に対するスタチンの有用性は十分に証明されているとは言えない．今後 EBM の観点からも医療経済的な視点からも，日本人におけるスタチン投与の有用性の検証が必要であると思われる．

今回の対象患者のうち 478 症例 (全症例の 84%) において，pravastatin 開始および調査時の血清脂質値が調査可能であった．Pravastatin 開始時の TC および LDL-C はそれぞれ 255 mg/dL および 162 mg/dL であった．この値は欧米および日本で行われた大規模臨床試験でのスタチン開始時での値とほぼ同値かやや低い値である[4~6,10~12]．今回，pravastatin の投与によって TC は 18%，LDL-C は 26%有意に低下した．Pravastatin を用いた大規模臨床試験における TC および LDL-C の低下率はそれぞれ 20%および 25%程度であることから[5,6,11,12]，それらの試験同様，本研究結果は pravastatin の良好なコレステロール低

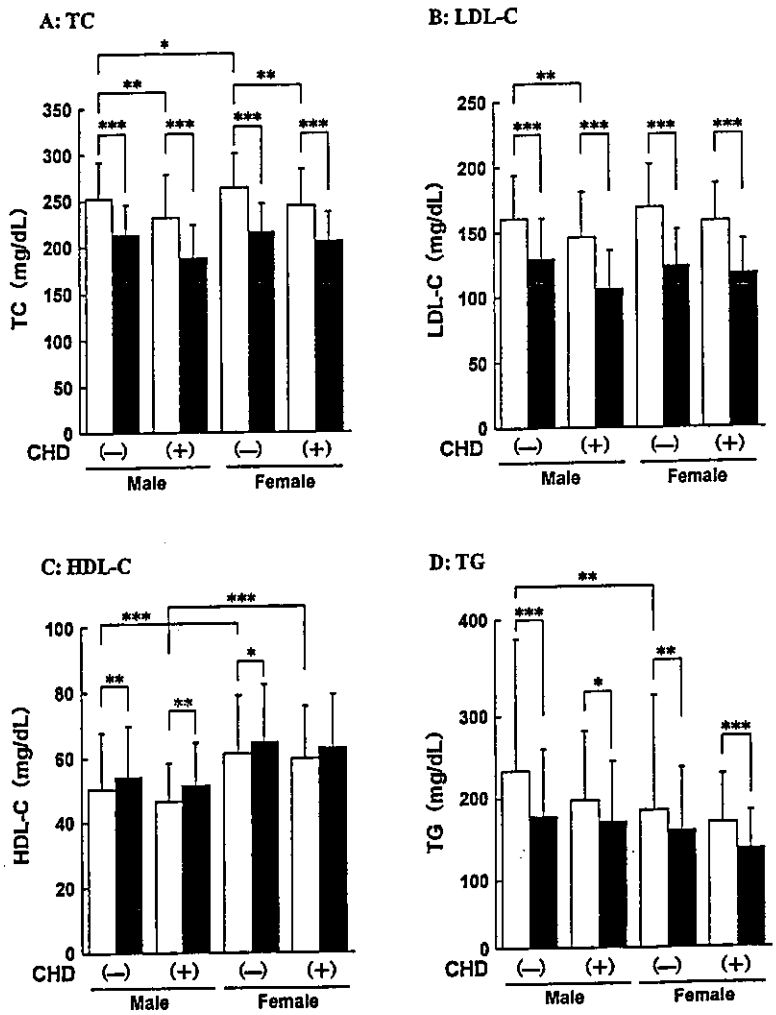

Fig. 5 Lipid profiles before (□) and after (■) the treatment with pravastatin in male and female patients with or without coronary heart disease (CHD)

TC : Total cholesterol, LDL-C : LDL cholesterol, HDL-C : HDL cholesterol, TG : triglyceride, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

Table 2 Laboratory data before and after the treatment with pravastatin in the patients with or without diabetes mellitus

Laboratory data	Diabetes mellitus	Number of patients	Before pravastatin	After pravastatin
AST	−	220	24.3±12.7	23.0±10.0
	+	132	22.8±9.2	22.8±13.9
ALT	−	221	23.0±10.0	21.7±16.8
	+	129	22.8±12.4	22.2±20.6
CPK	−	192	106±83	108±58
	+	116	99.8±93.3	115±106
BUN	−	208	16.4±5.2	16.9±6.2
	+	130	16.8±7.0	18.4±9.1**
s-Cre	−	199	0.819±0.300	0.838±0.336
	+	131	0.770±0.367	0.909±0.615***
BS	−	107	104±19	105±23
	+	118	163±74	153±84
HbA_{1c}	−	53	5.57±0.49	5.59±0.54
	+	104	7.64±1.74	7.37±1.61*

Values are mean ± SD, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$
AST : L-asparate aminotransferase, ALT : L-alanine aminotransferase, CK : creatine kinase,
s-Cre : serum creatinine, BUN : blood urea nitrogen, BS : blood glucose, HbA_{1c} : hemoglobin A_{1c}

Table 3 Demographic characteristics of the patients in the quartile treatment periods with pravastatin

	Periods with pravastatin [month]			
	0.9—22.1	22.1—50.8	50.9—87.2	87.5—174.5
Number of patinets	118	119	119	118
Male	56 (48%)	40 (34%)	49 (41%)	33 (28%)
Age* [years]	59.4±13.2	64.2±11.7	64.6±11.9	65.4±11.0
Smoking*	23 (19%)	21 (18%)	18 (15%)	16 (14%)
Risk factors				
Coronary heart disease	36 (31%)	30 (25%)	23 (19%)	21 (18%)
Diabetes mellitus	39 (33%)	34 (29%)	41 (34%)	48 (41%)
Hypertension	63 (53%)	79 (66%)	72 (61%)	76 (64%)

Values are number of patients or mean±SD.
( ) : % of numbers in the quartile treatment periods with pravastatin.
*Data at the point of the survey are presented.

下作用を示すものである．

今回興味深いことに，男女ともに虚血性心疾患の既往がある群では既往なし群に比べ，pravastatin はより低値の TC レベルから処方が開始されていることが明らかとなった．また虚血性心疾患の既往にかかわらず，女性に比べ男性でより低い TC から pravastatin の処方が開始されていた．このことは，処方者が虚血性心疾患発症リスクを考慮し，男性や虚血性心疾患の既往のある患者に対して，より低い TC から投与を開始したものと考えられる．

スタチン投与による臨床検査値の変動は，糖尿病の既往なし群では認められなかった．糖尿病を有する患者で pravastatin 服用後において HbA_{1c} が有意に低下していた．本研究では糖尿病の治療開始時期などの調査は行っていないため，HbA_{1c} が低下した理由は明らかではないが，pravastatin 服用期間中に糖尿病の治療が開始されたのではないかと思われる．さらに糖尿病を有する患者において腎機能検査値（s-Cre, BUN）の有意な上昇を認めた．このメカニズムは明らかではないが，糖尿病の合併症として腎機能障害の頻度は高く，非糖尿病患者群では pravastatin 投与によっても s-Cre と BUN の有意な変化は認められないことから，糖尿病の自然経過を反映するものかもしれない．

今回の調査は浜松医科大学附属病院の pravastatin 服用患者を対象とした．本研究結果は大学病院のような特定機能病院のものであり，直接わが国全体の処方動向と一致するものではないかもしれない．一般病院や診療所などにおける同様な調査の結果と併せて考慮する必要があるだろう．

さらに本研究では 2002 年 6 月から 1 年間の期間に pravastatin を投与されているほぼ全患者について調査し，2002 年 6 月からさかのぼって平均 4.5 年間の投与期間について調査した．したがって調査対象には，長期間投与されている患者と比較的最近投与が開始されている患者が混在している（Fig. 1）．このうちとくに長期間にわたって投与されている患者についてのデータの解釈には慎重でなければならない．すなわち数年前に投与が開始され，2002 年の 6 月から 1 年間の期間のいずれかの時点でも引き続き，pravastatin が投与されている患者は，数年前に投与開始となった患者の一部分と考えられ，死亡例，当該医療機関への来院を中止したもの，来院は続けているとしても副作用や十分な効果がみられないために投与を中止または変更したもの，または逆に血清脂質の正常化などの理由で治療を中止したものなどは，本研究の調査対象には含まれていない．これらの理由で調査対象に含まれていない患者の背景と，調査対象に含まれている長期にわたって投与が続けられている患者の背景が相違する可能性は否定できない．Pravastatin 服用期間に対して対象患者の背景因子を検討したところ，年齢および虚血性心疾患の既往率以外の因子に関しては明らかな傾向は認められなかった（Table 3）．平均年齢は服用期間が長くなるほど高い傾向が認められた．さらに虚血性心疾患の既往患者の割合は服用期間が短いほど増加する傾向が認められた．この理由として長期投与患者では虚血性心疾患発症にともなう他剤への変更または患者の死亡や転院が潜在する可能性が考えられる．したがって，今回の調査結果では pravastatin 服用患者の虚血性心疾患既往率を低く見積もっている可能性は否定できない．一方でこの結果は，最近になって pravastatin は一次予防に比べ二次

予防に対し積極的に用いられるようになったことを示しているのかもしれない．

結　論

本研究の対象患者においてpravastatinは血清コレステロール値を有意に低下しており，本剤の高脂血症治療における臨床的有用性が確認された．さらに処方者は心血管疾患発症リスクを考慮し，男性や虚血性心疾患の既往のある患者に対して，より低いTC値から投与を開始していることが明らかとなった．

一方，本研究では比較的虚血性心疾患発症リスクが低いと考えられる患者に対してpravastatin処方頻度が高いことが明らかとなった．虚血性心疾患の既往がない女性など低リスク患者に対するスタチン使用の有用性についてはいまだ十分に証明されているとは言えず，今後このような患者群に対するスタチン投与のエビデンス構築が必要と考えられる．

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29-0957

ピルジカイニドの血漿中濃度と臨床検査値および心電図変化

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【目的】クラスⅠ抗不整脈薬は血漿中薬物濃度の有効域が狭く副作用濃度と近接しているため、血漿中薬物濃度を測定しながら投与することが望ましい薬剤とされているが、現在のところ薬物治療モニタリング(TDM)は充分に行われていない。本研究ではピルジカイニド(Pil)投与中の患者における血漿中薬物濃度と臨床検査値および投与前後における心電図変化の関係を明らかにすることを目的とした。さらに、Pilの血漿中濃度が著しく高値であり副作用が認められた症例について報告する。

【方法】Pil服用中の患者21例を対象とし、血漿中薬物濃度をHPLC法を用いて測定した。また臨床検査値およびPil投与開始前後におけるQRS幅とQTc値の調査を行った。

【結果・考察】対象患者における血漿中Pil濃度は6.2-120.0μg/mLであり、そのうち4例(19%)が治療域よりも低値を、4例(19%)が高値を示した。また、投与量で補正した血漿中Pil濃度とクレアチニンクリアランスの間には相関を示す傾向が認められた(p=0.09)。さらに、Pil投与開始前後においてQRS幅とQTcには有意な変化は認められなかった。一方、血漿中Pil濃度が2.65μg/mLであった症例において、頭痛と口渇が認められ、QRS幅およびQTcが投与前に比べ延長していた。なお本症例においてPilの投与量減量に伴い血漿中薬物濃度は低下し、これらの症状は消失した。以上より、今回検討したPilの血漿中薬物濃度の範囲においては、Pilの投与により有意なQRS幅およびQTcの延長は認められないものの、血漿中薬物濃度が高値の症例で明らかな副作用が発現したことから、Pilの投与時にTDMを行うことが有用であると示唆された。