Vickers, S., Duncan, C.A., Chen, I.W., Rosegay, A., Duggan, D.E., 1990. Metabolic disposition studies on simvastatin, a cholesterol-lowering prodrug. Drug Metabolism and Disposition 18, 138–145.

Vickers, S., Duncan, C.A., Vyas, K.P., Kari, P.H., Arison, B., Prakash, S.R., Ramjit, H.G., Pitzenberger, S.M., Stokker, G., Duggan, D.E., 1990. In vitro and in vivo biotransformation of simvastatin, an inhibitor of HMG CoA reductase. Drug Metabolism and Disposition 18, 476–483.

Wang, J.S., Wen, X., Backman, J.T., Taavitsainen, P., Neuvonen, P.J., Kivisto, K.T., 1999. Midazolam alpha-hydroxylation by human liver microsomes in vitro: inhibition by calcium channel blockers, itraconazole and ketoconazole. Pharmacology and Toxicology 85, 157–161.

Wood, D., 2001. Asymptomatic individuals–risk stratification in the prevention of coronary heart disease. British Medical Bulletin 59, 3–16.

Yeo, K.R., Yeo, W.W., Wallis, E.J., Ramsay, L.E., 1999. Enhanced cholesterol reduction by simvastatin in diltiazem-treated patients. British Journal of Clinical Pharmacology 48, 610–615.

Yeo, K.R., Yeo, W.W., 2001. Inhibitory effects of verapamil and diltiazem on simvastatin metabolism in human liver microsomes. British Journal of Clinical Pharmacology 51, 461–470.

Original Article

Interaction between Amlodipine and Simvastatin in Patients with Hypercholesterolemia and Hypertension

Shinichiro NISHIO, Hiroshi WATANABE, Kazuhiro KOSUGE, Shinya UCHIDA, Hideharu HAYASHI*, and Kyoichi OHASHI

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.

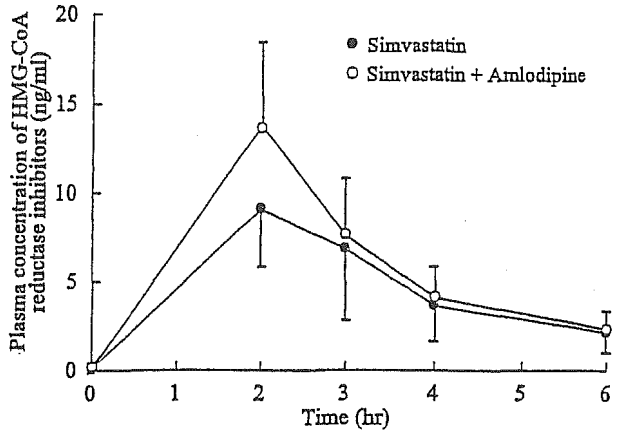

Fig. 1. *Time profiles of the mean plasma concentrations of HMG-CoA reductase inhibitors on the last day of 4 weeks of treatment with simvastatin (5 mg/day) or combined treatment with simvastatin (5 mg/day) and amlodipine (5 mg/day). Each point represents the mean±SD.*

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

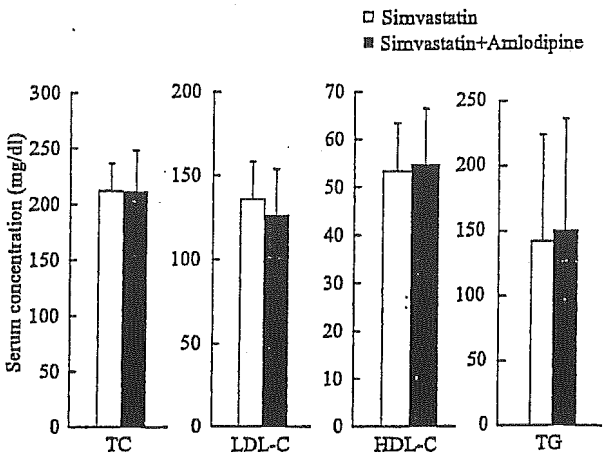

Fig. 2. *Mean levels of serum lipid parameters on the last day of 4 weeks of treatment with simvastatin (5 mg/day) or combined treatment with simvastatin (5 mg/day) and amlodipine (5 mg/day). TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol;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

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.

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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References

1. Gould KL, Casscells SW, Buja LM, Goff DC: Non-invasive management of coronary artery disease. Report of a meeting at the University of Texas Medical School at Houston. *Lancet* 1995; 346: 750–753.
2. Shepherd J: Preventing coronary artery disease in the West of Scotland: implications for primary prevention. *Am J Cardiol* 1998; 82: 57T–59T.
3. Tonkin AM: Management of the long-term intervention with pravastatin in ischaemic disease (LIPID) study after the scandinavian simvastatin survival study (4S). *Am J Cardiol* 1995; 76: 107C–112C.
4. Matsubara K, Yamamoto Y, Sonoyama K, *et al*: Current status of lipid management of hypertensive patients. *Hypertens*

Res 2003; **26**: 699–704.
5. Minami M, Atarashi K, Ishiyama A, Hirata Y, Goto A, Omata M: Effects of cholesterol-lowering therapy on pressor hyperreactivity to stress in hypercholesterolemic patients. *Hypertens Res* 2003; **26**: 273–280.
6. Wood D: Asymptomatic individuals—risk stratification in the prevention of coronary heart disease. *Br Med Bull* 2001; **59**: 3–16.
7. Gotto AM Jr: Risk factor modification: rationale for management of dyslipidemia. *Am J Med* 1998; **104** (Suppl 1): 6S–8S.
8. Williams D, Feely J: Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002; **41**: 343–370.
9. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary artery disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–1389.
10. Vickers S, Duncan CA, Chen IW, Rosegay A, Duggan DE: Metabolic disposition studies on simvastatin, a cholesterol-lowering prodrug. *Drug Metab Dispos* 1990; **18**: 138–145.
11. Vickers S, Duncan CA, Vyas KP, *et al*: *In vitro* and *in vivo* biotransformation of simvastatin, an inhibitor of HMG CoA reductase. *Drug Metab Dispos* 1990; **18**: 476–483.
12. Prueksaritanont T, Gorham LM, Ma B, *et al*: *In vitro* metabolism of simvastatin in humans: identification of metabolizing enzymes and effect of the drug on hepatic P450s. *Drug Metab Dispos* 1997; **25**: 1191–1199.
13. Neuvonen PJ, Kantola T, Kivisto KT: Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clin Pharmacol Ther* 1998; **63**: 332–341.
14. Kantola T, Kivisto KT, Neuvonen PJ: Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; **64**: 177–182.
15. Hsyu PH, Schultz-Smith MD, Lillibridge JH, Lewis RH, Kerr BM: Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. *Antimicrob Agents Chemother* 2001; **45**: 3445–3450.
16. Sutton D, Butler AM, Nadin L, Murray M: Role of CYP3A4 in human hepatic diltiazem *N*-demethylation: inhibition of CYP3A4 activity by oxidized diltiazem metabolites. *J Pharmacol Exp Ther* 1997; **282**: 294–300.
17. Jones DR, Gorski JC, Hamman MA, Mayhew BS, Rider S, Hall SD: Diltiazem inhibition of cytochrome P-450 3A activity is due to metabolite intermediate complex formation. *J Pharmacol Exp Ther* 1999; **290**: 1116–1125.
18. Watanabe H, Kosuge K, Nishio S, *et al*: Pharmacokinetic and pharmacodynamic interactions between simvastatin and diltiazem in patients with hypercholesterolemia and hypertension. *Life Sci* 2004; **76**: 281–292.
19. Kato J, Aihara A, Kikuya M, *et al*: Risk factors and predictors of coronary arterial lesions in Japanese hypertensive patients. *Hypertens Res* 2001; **24**: 3–11.
20. Ogihara T, Hiwada K, Morimoto S, *et al*: Guidelines for treatment of hypertension in the elderly—2002 revised version—. *Hypertens Res* 2003; **26**: 1–36.
21. Fukui T, Rahman M, Hayashi K, *et al*: Candesartan antihypertensive survival evaluation in Japan (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: rationale, design, and methods. *Hypertens Res* 2003; **26**: 979–990.
22. Abernethy D R: Pharmacokinetics and pharmacodynamics of amlodipine. *Cardiology* 1992; **80** (Suppl 1): S31–S36.
23. Kinnard DR, Harris M, Hossack KF: Amlodipine in angina pectoris: effect on maximal and submaximal exercise performance. *J Cardiovasc Pharmacol* 1988; **12** (Suppl 7): S110–S113
24. Hansson L, Hedner T, Lund-Johansen P, *et al*: Randomised trial of effects of calcium antagonists compared with diuretics and β-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000; **356**: 359–365.
25. Yamamoto Y, Sonoyama K, Matsubara K, *et al*: The status of hypertension management in Japan in 2000. *Hypertens Res* 2002; **25**: 717–725.
26. Eguchi K, Kario K, Shimada K: Differential effects of a long-acting angiotensin converting enzyme inhibitor (temocapril) and a long-acting calcium antagonist (amlodipine) on ventricular ectopic beats in older hypertensive patients. *Hypertens Res* 2002; **25**: 329–333.
27. Meredith PA, Elliott HL: Clinical pharmacokinetics of amlodipine. *Clin Pharmacokinet* 1992; **22**: 22–31.
28. Abernethy DR: The pharmacokinetics profile of amlodipine. *Am Heart J* 1989; **118**: 1100–1103.
29. Kuramoto K, Ichikawa S, Hirai A, Kanada S, Nakachi T, Ogihara T: Azelnidipine and amlodipine: a comparison of their pharmacokinetics and effects on ambulatory blood pressure. *Hypertens Res* 2003; **26**: 201–208.
30. Guengerich FP, Brian WR, Iwasaki M, Sari MA, Baarnhielm C, Berntsson P: Oxidation of dihydropyridine calcium channel blockers and analogues by human liver cytochrome P-450 IIIA4. *J Med Chem* 1991; **34**: 1838–1844.
31. Katoh M, Nakajima M, Shimada N, Yamazaki H, Yokoi T: Inhibition of human cytochrome P450 enzymes by 1,4-dihydropyridine calcium antagonists: prediction of *in vivo* drug-drug interactions. *Eur J Clin Pharmacol* 2000; **55**: 843–852.
32. Friedeward WT, Levy RI, Fredrickson DS: Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499–502.
33. Arnadottir M, Eriksson LO, Thysell H, Karkas JD: Plasma concentration profiles of simvastatin 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin. *Nephron* 1993; **65**: 410–413.
34. Josefsson M, Zackrisson AL, Ahlner J: Effect of grapefruit juice on the pharmacokinetics of amlodipine in healthy volunteers. *Eur J Clin Pharmacol* 1996; **51**: 189–193.
35. Prueksaritanont T, Vega JM, Zhao J, *et al*: Interactions between simvastatin and troglitazone or pioglitazone in healthy subjects. *J Clin Pharmacol* 2001; **41**: 573–581.
36. Ma B, Prueksaritanont T, Lin JH: Drug interactions with calcium channel blockers: possible involvement of metabolite-intermediate complexation with CYP3A. *Drug Metab Dispos* 2000; **28**: 125–130.

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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．

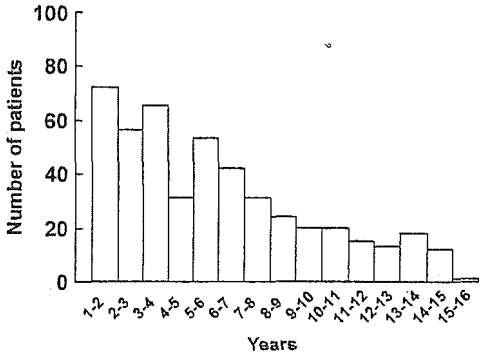

Fig. 1 Periods treated with pravastatin

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

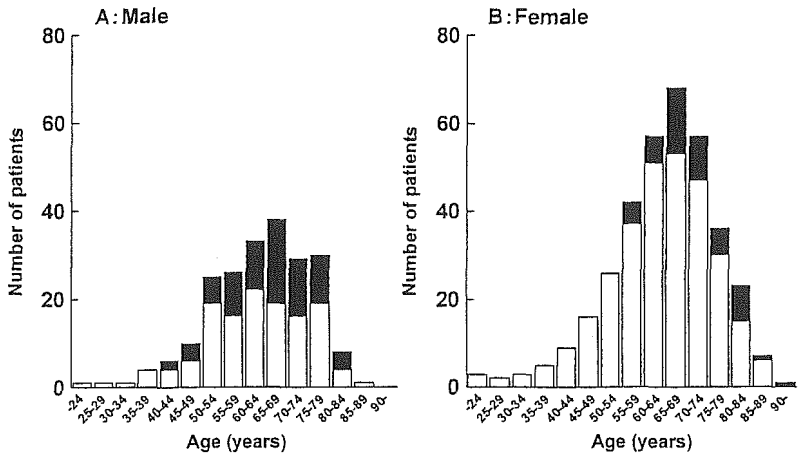

Fig. 2 Number of male (A) and female (B) patients with coronary heart disease (CHD, ■) or without CHD (□)

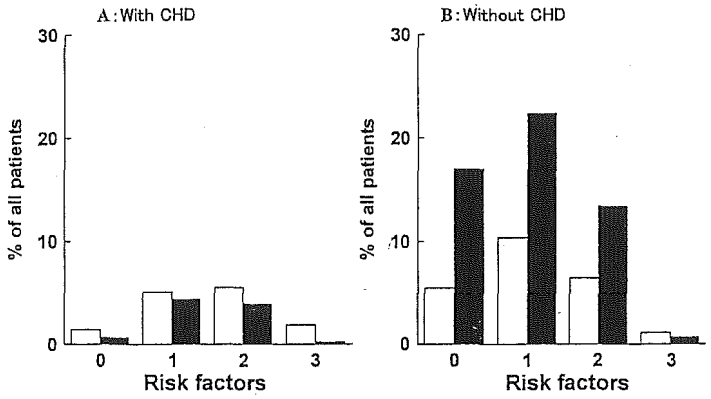

Fig. 3 Number of risk factors (smoking, diabetes mellitus and hypertension) in the patients with (A) and without (B) coronary heart disease (CHD)
Data are % of all patients (n=569).
□ : Male, ■ : Female

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

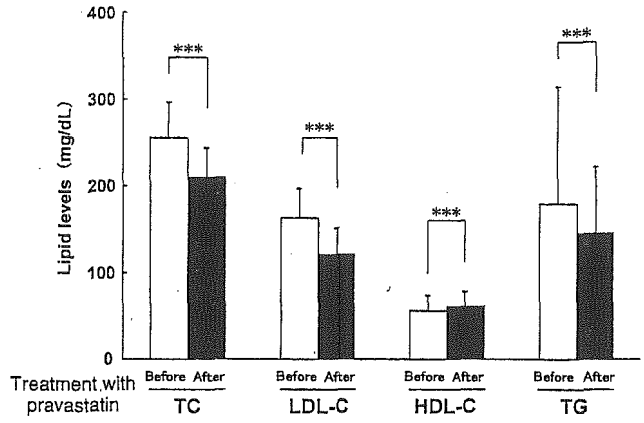

Fig. 4 Lipid profiles in the patients before (□) and after (■) the treatment with pravastatin
TC : Total cholesterol, LDL-C : LDL cholesterol, HDL-C : HDL cholesterol, TG : triglyceride, $***p<0.001$

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

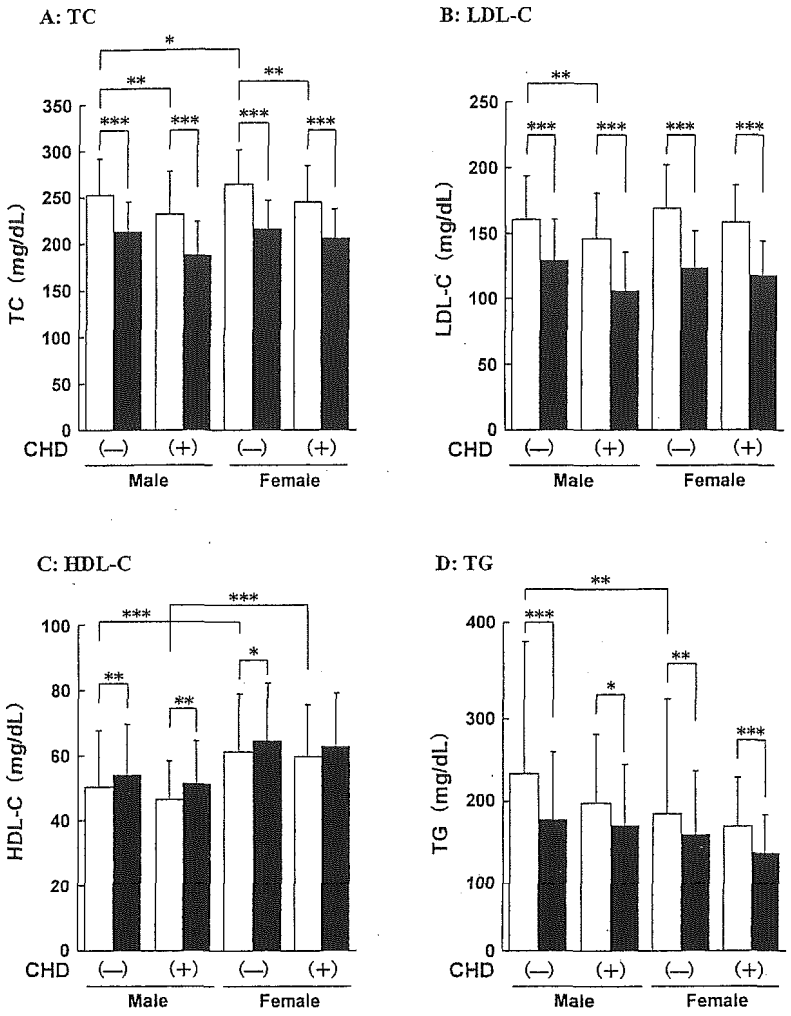

Fig. 5 Lipid profiles before (□) and after (■) the treatment with pravastatin in male and female patients with or without coronary heart disease (CHD)

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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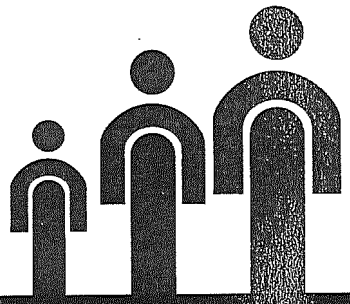
文　献

1) Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA* 1986；**256**：2835-8.
2) Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986；**256**：2823-8.
3) 清原裕地．日本動脈硬化学会・日本糖尿病学会合同委員会．地域住民中の糖尿病者における循環器疾患発症とその危険因子の関連―久山町研究―．*糖尿病合併症* 2000；**14**：80-4.
4) Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995；**333**：1301-7.
5) Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996；**335**：1001-9.
6) Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998；**339**：1349-57.
7) Saito I, Folsom AR, Aono H, Ozawa H, Ikebe T, Yamashita T. Comparison of fatal coronary heart disease occurrence based on population surveys in Japan and the USA. *Int J Epidemiol* 2000；**29**：837-44.
8) 渡邉裕司．Evidence Based Medicine（EBM）と臨床薬理．エビデンスを使う．循環器領域―臨床決断とエビデンス．*臨床薬理* 2003；**34**：223-7.
9) 日本クリニカル・エビデンス編集委員会（監修）．*クリニカル・エビデンス ISSUE9 日本語版*．日経BP社，2004：166-8.
10) Pravastatin use and risk of coronary events and cerebral infarction in Japanese men with moderate hypercholesterolemia：the Kyushu Lipid Intervention Study. *J Atheroscler Thromb* 2000；**7**：110-21.
11) Ito H, Ouchi Y, Ohashi Y, Saito Y, Ishikawa T, Nakamura H, Orimo H. A comparison of low versus standard dose pravastatin therapy for the prevention of cardiovascular events in the elderly：the pravastatin anti-atherosclerosis trial in the elderly (PATE). *J Atheroscler Thromb* 2001；**8**：33-44.
12) Matsuzaki M, Kita T, Mabuchi H, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, Itakura H, J-LIT Study Group. Japan Lipid Intervention Trial. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia. *Circ J* 2002；**66**：1087-95.



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Pharmacogenetics

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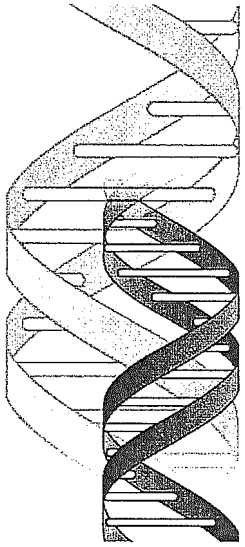
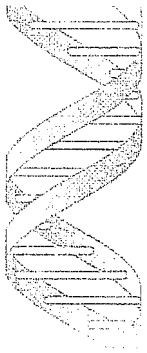


Pharmacogenetics

Towards improving treatment with medicines



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Geneva, 12 January 2005

Juhana E. Idänpään-Heikkilä, MD, PhD
Secretary-General, CIOMS

Preface

The notion that genetic factors can be responsible for altered drug response in some patients evolved in the late 1950s. The term 'pharmacogenetics' was coined in 1959 to describe a new scientific discipline that dealt with inherited differences in the response to drugs. It has been suggested that selection of drug therapy based on the genetic make-up of a patient may result in not only an improved therapeutic response but also a clinically important reduction in adverse drug reactions.

Increasingly, sponsors of new drugs are integrating pharmacogenetics in their drug development programmes. The outcome of this integration will present challenges to the traditional paradigms for drug development, regulatory evaluation of safety and efficacy and clinical use of drugs. Ethical, legal and pharmacoeconomic issues are also integral to the debate.

Pharmacogenetics is still an evolving discipline and a very active area of research. It promises to revolutionise therapeutics by 'personalising medicine'. The term 'personalised medicine' is potentially misleading and may be interpreted to mean that drugs are *developed* for individual patients. A term that we prefer to use is 'individually targeted therapy'. In principle, genotype-based individually targeted prescribing ought to be more effective at improving response rates and decreasing the burdens of adverse drug reactions.

The extent to which this promise of pharmacogenetics is fulfilled remains to be seen. The experience to date is mixed with a few successes but many frustrations. Discovering highly predictive genotype-phenotype associations during drug development and demonstrating their clinical validity and utility in well-designed prospective clinical trials will no doubt better define the role of pharmacogenetics in future clinical practice. In the meantime, pharmacogenetic research deserves support from all concerned but without unrealistic expectations.

This Report, an outcome of inspiring discussions among a number of senior scientists from drug regulatory authorities, pharmaceutical companies and academia, addresses many of these issues in detail. It reflects their views and visions today and expectations for the future. The reader will find that there is duplication of information in various chapters. This is deliberate. The CIOMS Working Group on Pharmacogenetics considered that each chapter should be self-standing with its own references.

CIOMS and its Working Group on Pharmacogenetics hope that readers will enjoy this contribution to the ongoing discussions and debate.

Contents

Disclaimer

Although most chapters enjoyed an undivided support, there were others where unanimity was not possible. Therefore, the views expressed in this Report should be considered majority-based consensus views and not necessarily the unanimous views of all the members of the CIOMS Working Group on Pharmacogenetics (*see Annex 1*) or of the affiliations served by these members.

Chapter 1

Introduction and Problem Statement

1. Introduction

The latter half of the last century has witnessed the development of most of the drugs that are used today. The introduction of these drugs has led to dramatic changes in the practice of medicine since it has allowed for the first time the effective treatment of many common diseases such as hypertension, angina pectoris, depression, schizophrenia, lymphomas and leukaemias to name only a few.

Right from the beginning of modern drug therapy it was observed that there was substantial variability among patients both in therapeutic efficacy and the occurrence of side effects. Moreover, for all major classes of drugs (angiotensin converting enzyme inhibitors, ß-adrenoreceptor antagonists, selective serotonin reuptake inhibitors, tricyclic antidepressants, statins and ß-agonists) a significant proportion of patients will not respond, or respond only partially, when standard doses of the particular drug are administered. The realisation that dose was a poor predictor of therapeutic response stimulated efforts in elucidating the mechanisms responsible.

From these studies it became apparent that the rate at which drugs are eliminated from the body showed substantial interindividual differences. In particular, drug metabolising enzymes were identified to play a pivotal role in the elimination process of most drugs. Since individual optimisation of dosage with such drugs in clinical practise is difficult, there follows sub-optimal treatment, prolonged periods of trial and error and non-compliance with a consequential increase in morbidity, mortality and costs. Therefore, considerable efforts have been expended to identify the mechanisms underlying the marked variability of drug response. As possible mechanisms, heterogeneity of the disease and such clinical variables as age, gender, diet, co-administration of drugs, renal and hepatic function were identified. In addition to these factors it was recognised that genetic factors involved in drug disposition (absorption, distribution, metabolism and elimination) or drug action (receptors and signalling pathways) can modify drug response or are risk factors for adverse drug reactions.

2. Birth of pharmacogenetics

Genetic factors have been suggested, depending on the drug, to account for 20 to 95% of the variability in drug disposition and effects [1, 2]. The concept that genetic factors which alter the pharmacokinetics and pharmacodynamics of drugs can be responsible for altered drug response in some patients evolved in the late 1950s. At that time it was demonstrated that an inherited deficiency of glucose-6-phosphate dehydrogenase was responsible for the severe haemolysis observed in some patients when exposed to the antimalarial primaquine. This discovery also provided an explanation for why primaquine-induced haemolysis mainly affected the African Americans – this deficiency occurred with a much higher frequency in this ethnic group and was rarely observed in Caucasians of Northern, Western and Eastern European descent. [3]

In 1959, Vogel coined the term 'pharmacogenetics' to describe a new scientific discipline that dealt with inherited differences in the response to drugs [4]. In recent years, the term pharmacogenomics has been introduced to describe the progressive transition from genetics to genomics realising that the genome is more than the sum of its genes. It introduces an additional element of a genome-wide approach to identify genes that contribute to a specific disease. *Pharmacogenetics* is defined as the study of interindividual variations in DNA sequence related to drug disposition (pharmacokinetics) or drug action (pharmacodynamics) that can influence clinical response. In contrast, *pharmacogenomics* is defined more broadly as the application of genomic technologies to elucidate disease susceptibility, drug discovery, pharmacological function, drug disposition and therapeutic response. This approach will lead to a new classification(s) of diseases at the molecular level. Moreover, identification of new disease genes will provide new drug targets. Of the 30,000 diseases presently known, there is either no drug treatment or improved drug treatment is needed for more than a 100 to 150 major common diseases. The drugs used today are targeted at approximately 500 pharmacologically active biological targets and there is a great hope that there are at least 3,000 to 10,000 'drugable' targets [5].

3. Pharmacogenetics and therapeutics

Severe adverse drug reactions (ADRs) such as hepatotoxicity or drug-induced arrhythmias continue to be a significant problem both during the development and in the postmarketing phase of new drugs. ADRs increase morbidity and mortality and are associated with considerable cost

to the healthcare system. The timeliness of this problem is emphasised by a recent survey indicating that adverse drug reactions may be responsible for over 100,000 deaths annually in the US and account for about 5% of all hospital admissions [6]. Recent studies indicate that genetic factors play a role in the pathogenesis of both predictable and unpredictable ADRs. It has been suggested that drug therapy based on the individual genetic make-up of a patient may not only result in an improved response but also in a clinically important reduction in ADRs. For example, Philips and co-workers identified in their systematic review 27 drugs frequently cited in ADR studies [7]. Among these drugs, 59% were metabolised by at least one enzyme with a variant allele known to cause poor metabolism. In contrast, only 7% to 20% of randomly selected drugs were metabolised by enzymes that are known to be expressed polymorphically. This analysis suggests that genetic variability in drug metabolising enzymes is a contributor to the incidence of ADRs.

4. Pharmacogenetics and drug development

Worldwide, new drug applications are declining although the number of new chemical entities (NCEs) screened has increased with the use of modern high throughput technology. Ninety percent of new candidates selected from the preclinical phase fail during the clinical development. In 80% of those drugs entering the clinical trials, poor response or side effects are the reasons for terminating development. Thus, there is an urgent need to increase the success rate. One way of improving the success rate is to identify potential responders and non-responders to the drug under investigation on the basis of genetic testing before inclusion into a clinical trial. It is hoped that this approach will not only increase the success rate but also lead to a reduction in the number of patients required to demonstrate efficacy of the drug. As a consequence, the time for the clinical phase of development could be shortened and the costs reduced. However, there are safety-related limitations to this approach. At least one to two drugs are withdrawn every year from the market because of severe ADRs. Recent examples include troglitazone, mibefradil, some newer fluoroquinolones and cerivastatin. Since only a very small number of patients experienced these severe ADRs, it is quite likely that genetic factors predispose these patients to toxicity. Withdrawal of a drug is associated with enormous financial costs to the pharmaceutical industry since it costs about 500 to 700 million Euros to develop a drug and take it through its various preclinical and clinical phases. The industry, and indeed the society, cannot afford such withdrawals, as recent data indicate that the fall in the num-

ber of new drugs approved in the US is reaching a crisis point and that new drug applications are down worldwide. Identification of genetic factors associated with severe ADRs could save some of these drugs [8-10].

5. Pharmacogenetics and targeted prescribing

With the complete sequence of the human genome now available, it is hoped that better targeted medicine will soon become a reality. The expectations are that with the use of genomic information, we will be able to better predict an individual's likely response to a drug and select the appropriate dose of the drug. This would allow achieving the optimal therapeutic response, avoiding therapeutic failure and minimising side effects and toxicity. Although many genes responsible for inherited differences in the metabolism, transport and action of drugs have been identified, this new knowledge has not been translated into clinical practice. With the exception of a few examples of drug metabolising enzymes, the contribution of genetic polymorphisms to individual differences in drug effects and toxicity are not well understood. Moreover, most of these studies have focused on the consequences of a single gene polymorphism for an altered drug response. This approach, however, neglects the fact that drug response phenotype like most disease phenotypes is a complex polygeneic trait with non-genetic factors contributing to the manifestation of the phenotype [11].

6. Limitations of pharmacogenetics

The extent to which genetic factors contribute to drug response/toxicity phenotype will depend on whether the candidate gene is a gene of major, moderate or minor effect. There are also misconceptions with respect to the information provided by a pharmacogenetic test. Even in the case of a gene with maximum effect, the presence or absence of a mutation will not provide a straight forward 'yes' or 'no' answer but rather the likelihood that in a subject with a given mutation, an event will or will not occur. The highest positive predictive value of a genetic test will be observed for genes with major effect. In the case of drug metabolising enzymes, mutations leading to a loss of function will result in higher drug concentrations. If these higher drug concentrations are associated with toxicity, the likelihood that a patient who has this genotype will develop toxicity is increased provided the patient is prescribed the same dose as the remainder of the patients who carry the wild type of the gene. However, the negative predictive value (likelihood that a patient without the mutation will not have toxicity) can be rather poor if non-genetic factors that lead to high drug concentrations (which are associated with drug toxicity) are neglected. If a patient who carries a wild type gene is concomitantly treated with a drug that inhibits the enzyme, the patient will develop the phenotype of high concentration that is usually associated with the presence of two mutant alleles, a phenomenon known as 'phenocopying'. Neglecting the impact of non-genetic factors on the manifestation of a drug response phenotype has led to claims that genotyping for the deficient alleles of thiopurine S-methyltransferase (TPMT) has a poor predictive value for the development of severe myelosuppression, which is seen with the use of 6-mecaptourine or azathioprine. It is vital therefore that pharmacogenetic information is used to improve prescribing decisions and considered alongside other key information in a holistic manner.

One of the major limitations, which has prevented the use of pharmacogenetic testing in the clinical setting, is the lack of prospective clinical trials demonstrating that pharmacogenetic testing can assist in the selection of the appropriate drug and dose for the individual patient in order to achieve the optimal therapeutic response, avoid therapeutic failure and minimise side effects and toxicity. The current pharmacogenetic research being undertaken by both the private and the public sectors will need to address this deficit.

With the rapid progress being made in molecular genetics, more and more genes that can alter drug response will be identified. Since drug response involves several genes, the positive and negative predictive values of pharmacogenetic testing will be improved by combining information from each of the contributing genes. Thus with the advances made in technology, the cost of genotyping will become affordable and it should be possible to establish pharmacogenetics for optimising drug development and drug therapy.

REFERENCES

[1] Evans WE, McLeod HL.
Pharmacogenomics – drug disposition, drug targets and side effects.
N Eng J Med. 2003; 348: 538-549

[2] Weinshilboum R.
Inheritance and drug response.
N Engl J Med. 2003; 348: 529-537

[3] Beutler E.
Drug induced haemolytic anaemia.
Pharmac Rev. 1969; 21: 73-103