Influence of Age and Gender on the Plasma Profiles of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitory Activity Following Multiple Doses of Lovastatin and Simvastatin

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The effects of age and of gender on the plasma profiles of HMG-CoA reductase inhibitors following separate once-a-day dosage regimens (17 days) of lovastatin (80 mg/day) and simvastatin (40 mg/day) were studied in hypercholesterolemic patients. In general, plasma concentrations of active and total HMG-CoA reductase inhibitors were higher in elderly individuals (age, 70 to 78 years) and in females for both drugs. However, the T_{max} of these inhibitors was not significantly affected by either age or gender. Following the last dose of lovastatin, the mean steady-stage plasma concentrations of total and active HMG-CoA reductase inhibitors were 30–60% higher in the elderly than in young individuals (age, 19 to 30 years). Also, the mean plasma concentrations were 20–50% higher in female than in male patients. Similarly, following the last dose of simvastatin, the mean plasma concentrations of HMG-CoA reductase inhibitors were 40–60% higher in the elderly than in young patients and were 20–50% higher in female than in male patients. These age- and gender-related differences do not appear to be large enough to warrant modification of dosage regimens, because plasma concentrations of these inhibitors are not necessarily indicative of efficacy and the therapeutic windows for lovastatin and simvastatin are broad.

KEY WORDS: lovastatin; simvastatin; plasma levels; elderly; gender effect.

INTRODUCTION

Lovastatin (I) and simvastatin (II) are cholesterol-lowering agents used to treat hypercholesterolemia (1,2). As oral lactone prodrugs, they hydrolyze *in vivo* to their corresponding β-hydroxyacids (III and IV), which are potent inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and thus of de novo cholesterol sythesis. In hypercholesterolemic patients, lovastatin and simvastatin are generally well tolerated and cause substantial reductions in serum concentrations of low-density lipoprotein cholesterol (3–8).

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The systemic elimination of many agents is decreased in the elderly population, leading to higher plasma concentrations and hence the potential for increasing incidence of adverse effects (9,10). Gender-related differences in drug disposition in humans have also been reported for a number of drugs (11,12). Thus, it is important to study the effects of age and gender on the plasma profiles of HMG-CoA reductase inhibitors in man following multiple doses of lovastatin or simvastatin. This report presents the results of such a study.

MATERIALS AND METHODS

Clinical Study. After giving written consent, two groups of hypercholesterolemic patients participated in a two-period crossover study. One group consisted of 16 (7 males, 9 females) elderly patients between 70 and 78 years of age, weighing between 42.7 and 101.4 kg. The other group consisted of 18 (9 males, 9 females) young patients between 19 and 30 years of age, weighing between 53.2 and 109.1 kg. The inclusion criteria included patients whose age is either ≥70 years or between 18 and 30 years, patients with primary hypercholesterolemia with low-density lipoprotein (LDL) cholesterol on a diet above 160 mg/dl, and patients weighing within ±20% of their ideal body weights for their ages and heights. The exclusion criteria included pregnant women or nursing mothers; poor mental function; plasma triglycerides >300 mg/dl; hyperlipidemia of Type I, III, IV, or V; a history of drug or alcohol abuse; use of any lipid-lowering drugs within 42 days or any drugs within 7 days prior to the start of this study; regular use prior to the start of the study of any drugs known to affect rates of drug metabolism or elimination; cigarette smoking, if more than 10 cigarettes per day prior to or during the study; current use of oral contraceptives or other systemic hormonal medication; impaired hepatic function; symptomatic coronary heart disease; diabetes mellitus; secondary hypercholesterolemia due to hyperthyroidism, the nephrotic syndrome, or any other cause; and partial ileal bypass.

To ensure that the steady state of HMG-CoA reductase inhibitors was reached, each group received 80 mg of lovastatin (Mevacor; Merck Sharp & Dohme, West Point, PA) once a day for 17 days and 40 mg of simvastatin (Zocor; Merck Sharp & Dohme) once a day for another 17 days. The washout period between these two treatments was at least 4 weeks to ensure that the concentrations of HMG-CoA reductase recover to normal level. On days 1 through 5 and days 15 and 16 of each period, patients reported to the study center after an overnight fast. Drug was administered orally in the morning each day with 200 ml of water. On days 6 through 14 of each period, patients took their drug at home at 0800 hr after an overnight fast. On day 17 patients reported to the study center after an overnight fast. Two hours after taking the allocated treatment, patients were given a liquid breakfast. Four hours after taking the drug, they were provided a light lunch. Dinner was also supplied at about 1730 to 1800 hr. Blood samples (5 ml each) were collected in heparinized tubes at 0 hr only (predose) on days 1–5, 15, and 16. Multiple blood samples were taken on day 17 at time 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hr postdose.

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Plasma was obtained from each blood sample, frozen, and maintained frozen at −20°C until analysis.

Analytical Method. An enzymatic assay method was used to determine plasma concentrations of active and total (active plus potentially active) HMG-CoA reductase inhibitors (13). An aliquot of each sample was subjected to alkaline hydrolysis to determine the concentration of total inhibitors. Concentrations of active inhibitors were assayed in unhydrolyzed samples. The inhibitory activity was measured against either III or IV as a standard. Each β-hydroxyacid standard was used in its ammonium salt form and all results are expressed as nanogram equivalent per milliliter. The lower limit of quantitation in this assay was 5 ng Eq/ml for the ammonium salts of the β-hydroxyacids of lovastatin and simvastatin. The method is suitable for quantification of active and total HMG-CoA reductase inhibitors over a concentration range of 5–100 ng Eq/ml. The interday precision and accuracy values are 3.5–13.4% relative standard deviation and 97–112%, respectively.

Pharmacokinetic Analysis. The observed maximum concentration of HMG-CoA reductase inhibitors (C_{max}), the observed time of maximum inhibitory activity (T_{max}), and the area under the plasma profile of HMG-CoA reductase inhibitors (AUC) were determined from plasma data. The AUC values were calculated using the trapezoidal rule from time 0 to 24 hr after the last dose of study drug. The AUC and C_{max} ratios were calculated from individual values in elderly patients to those in young patients and in female patients to those in male patients. Comparisons of AUC, C_{max}, or T_{max} between elderly and young patients and between female and male patients were made using analysis of variance with a two-way general linear model (GLM) in SAS with factors age and gender and their interaction. The differences of these comparisons were considered significant at $P < 0.05$.

RESULTS AND DISCUSSION

Eighteen young patients, nine elderly female patients, and seven elderly male patients were enrolled in this study. In total, thirty-four patients entered the study. The statistical analyses were based on the data from these 34 patients who completed the crossover study. Mean plasma concentration profiles of HMG-CoA reductase inhibitors (active and total) in elderly and young patients receiving 80 mg/day lovastatin for 17 days are displayed in Figs. 1 and 2, respectively. Plasma concentrations of HMG-CoA reductase inhibitors reached steady state within 5 days postdose. Also, secondary peaks were evident in the plasma profiles of most patients, suggesting that these HMG-CoA reductase inhibitors undergo enterohepatic recycling.

The mean values of steady-state AUC, C_{max}, T_{max}, and ratios of mean AUC and C_{max} on day 17 in patients receiving lovastatin are summarized in Table I. The mean AUC value for the total inhibitors was approximately 1.4 times higher ($P > 0.05$) in the elderly females than in the young females and 1.6 times higher ($P < 0.05$) in the elderly males than in the young males, while the corresponding mean C_{max} value was 1.7 ($P < 0.05$) and 1.4 times higher ($P > 0.05$), respectively. Although the mean values of AUC and C_{max} for the total inhibitors were approximately 1.2–1.4 and 1.1–1.4 times higher, respectively, in the female patients than in the male patients, these differences are not statistically significant. Similar results were also obtained for active inhibitors except that the difference in C_{max} value of active inhibitors between elderly females and elderly males was statistically significant and the difference in AUC value of active inhibitors between elderly males and young males was not statistically significant. Thus, following multiple doses of lovastatin, there were apparent effects of age and gender on plasma concentrations of HMG-CoA reductase inhibitors. In

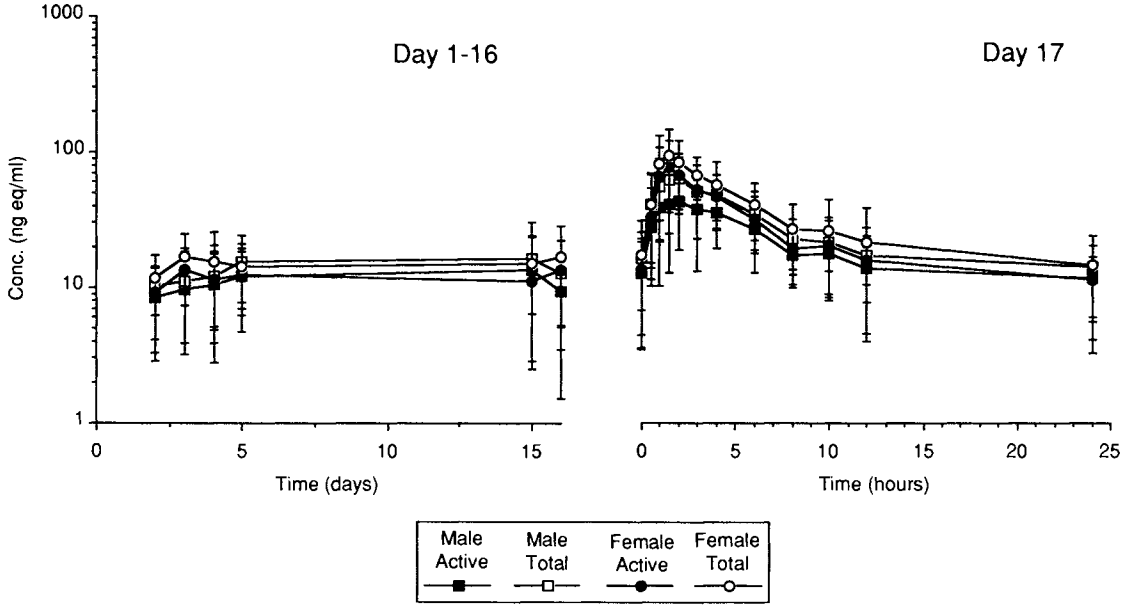

Fig. 1. Mean plasma concentrations of HMG-CoA reductase inhibitors on various days in elderly patients receiving 80 mg/day lovastatin for 17 days.

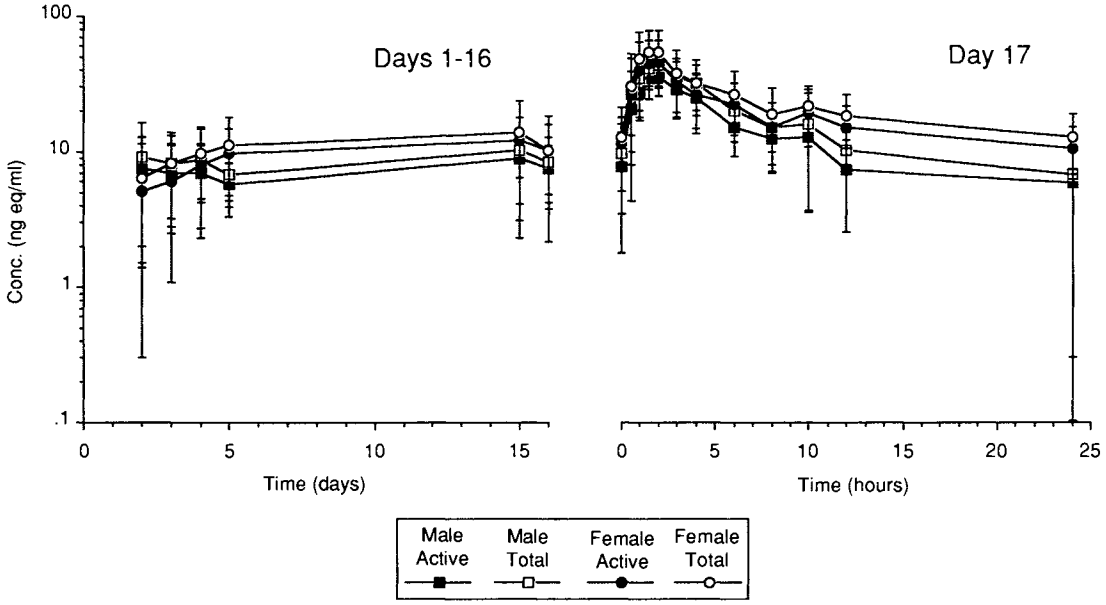

Fig. 2. Mean plasma concentrations of HMG-CoA reductase inhibitors on various days in young patients receiving 80 mg/day lovastatin for 17 days.

all cases, the T_{max} of active inhibitors were similar and averaged between 1.4 and 2.0 hr. The mean value of T_{max} of total inhibitors in young males was slightly larger (but not statistically significant) than that in young females and elderly males, while there was not much difference ($P > 0.05$) in T_{max} between elderly females and males or between elderly and young females.

Mean steady-state plasma concentration profiles of HMG-CoA reductase inhibitors (active and total) in elderly and young patients receiving 40 mg/day simvastatin for 17 days (data not shown) are similar to those observed following multiple doses of lovastatin except that predose plasma concentrations of total or active HMG-CoA reductase inhibitors in these patients were generally below the lower limit of

Table I. Summary of Mean Pharmacokinetic Parameters for HMG-CoA Reductase Inhibitors in Patients Following 80-mg Daily Doses (for 17 Days) of Lovastatin

	Active inhibitors			Total inhibitors		
	Female	Male	Ratio,[a] female/male	Female	Male	Ratio,[a] female/male
			Elderly patients			
C_{max} (ng Eq/ml)	88.1 ± 38.6	50.3 ± 23.4	1.78*	103.6 ± 46.8	72.9 ± 29.8	1.43
T_{max} (hr)	1.8 ± 0.7	1.9 ± 1.2	—[b]	1.9 ± 0.7	1.6 ± 0.8	—
AUC (ng Eq · hr/ml)	592.2 ± 257.8	473.7 ± 221.5	1.30	763.0 ± 394.9	622.7 ± 247.3	1.22
			Young patients			
C_{max} (ng Eq/ml)	53.0 ± 22.0	40.7 ± 5.9	1.21	60.8 ± 25.8	49.6 ± 8.3	1.14
T_{max} (hr)	1.4 ± 0.5	2.0 ± 0.9	—	1.3 ± 0.6	3.1 ± 2.9	—
AUC (ng Eq · hr/ml)	447.6 ± 157.8	305.2 ± 115.7	1.48	538.7 ± 205.5	385.3 ± 107.3	1.35

	Ratio[a]	
	Elderly female/young female	Elderly male/young male
Active inhibitors		
C_{max} (ng Eq/ml)	1.68*	1.14
AUC (ng Eq · hr/ml)	1.33	1.52
Total inhibitors		
C_{max} (ng Eq/ml)	1.73*	1.38
AUC (ng Eq · hr/ml)	1.40	1.56*

[a] Geometric mean ratio.
[b] Not applicable.
* $P < 0.05$.

quantitation of the assay method (5 ng eq/ml) and secondary peaks were not as evident as those for lovastatin.

The mean values of AUC, C_{max}, T_{max}, and ratios of mean AUC and C_{max} on day 17 in patients receiving 40 mg daily of simvastatin are summarized in Table II. The mean values of AUC and C_{max} for the total inhibitors were approximately 1.5 and 1.3 times higher, respectively (but not statistically significant), in the elderly females than in the young females and 1.6 and 1.5 times higher ($P < 0.05$), respectively, in the elderly males than in the young males. Similarly, the mean AUC value for the total inhibitors in the female patients was 1.2–1.3 times higher (not statistically significant) than that in the male patients, whereas the mean C_{max} value was about 1.5 ($P > 0.05$) and 1.7 ($P < 0.05$) times higher in the elderly and young females, respectively, than in the corresponding male patients. The AUC and C_{max} values of active inhibitors behaved similarly: only the difference in C_{max} value between the female patients and the male patients was statistically significant. Thus, following multiple doses of simvastatin, there were apparent effects of age and gender on values of AUC and C_{max} for total and active HMG-CoA reductase inhibitors. In all cases, the T_{max} of total and active inhibitors was similar and averaged between 1.1 and 1.4 hr.

In rats, simvastatin is extensively metabolized in the liver (14). It has been suggested previously that the gender-related differences in the utilization of microsomal metabolic pathways might explain the higher plasma levels of ^{14}C-metabolites observed in female rats than male rats after oral dosing with ^{14}C-simvastatin (14). Recently, simvastatin was shown to be more effectively metabolized by the liver microsomes of male rats than females (15). Thus, it is possible that the trend toward higher concentrations of HMG-CoA reductase inhibitors in female patients after multiple dosing with simvastatin or lovastatin might be attributed to the gender-related differences in the utilization of microsomal metabolic pathways.

Age-related differences in pharmacokinetics of many drugs have been attributed mainly to alterations in drug distribution, metabolism, and/or elimination (9–12). Both lovastatin (16) and simvastatin (14) are highly protein-bound but largely extracted by the liver and show a very pronounced hepatic first-pass metabolism. Little lovastatin or simvastatin, their respective hydroxy acids, or other metabolites are available to be excreted by the kidneys. The metabolites of both drugs are preferentially eliminated in bile (17). The hepatic clearances and consequently the plasma concentrations of HMG-CoA reductase inhibitors will depend on the hepatic blood flow, liver size, bile flow, and intrinsic clearance. In humans, there is little doubt that both liver blood flow and liver size decrease with age (18). Conversely, no similar age-related decline in drug metabolizing enzymes, which are related to intrinsic clearance, appears to occur (19). Thus, it appears that changes in liver blood flow and liver size and possibly bile flow might be the main reason for the observed age-related differences in plasma concentrations of HMG-CoA reductase inhibitors following multiple doses of lovastatin and simvastatin.

In conclusion, following a 17-day regimen of lovastatin 80 mg/day, age- and gender-related differences in steady-

Table II. Summary of Mean Pharmacokinetic Parameters for HMG-CoA Reductase Inhibitors in Patients Following 40-mg Daily Doses (for 17 Days) of Simvastatin

	Active inhibitors			Total inhibitors		
	Female	Male	Ratio,[a] female/male	Female	Male	Ratio,[a] female/male
			Elderly patients			
C_{max} (ng Eq/ml)	92.9 ± 35.6	58.1 ± 23.4	1.60*	124 ± 52	83.0 ± 26.1	1.45
T_{max} (hr)	1.2 ± 0.6	1.1 ± 1.2	—[b]	1.2 ± 0.5	1.2 ± 0.8	—
AUC (ng Eq · hr/ml)	280 ± 162	187 ± 101	1.52	351 ± 169	280 ± 87	1.21
			Young patients			
C_{max} (ng Eq/ml)	73.1 ± 18.7	45.8 ± 19.5	1.68*	91.8 ± 37.2	56.5 ± 24.7	1.66*
T_{max} (hr)	1.4 ± 0.7	1.4 ± 1.0	—	1.2 ± 0.3	1.4 ± 1.0	—
AUC (ng Eq · hr/ml)	193 ± 119	130 ± 32	1.34	271 ± 218	172 ± 49	1.30

	Ratio[a]	
	Elderly female/young female	Elderly male/young male
Active inhibitors		
C_{max} (ng Eq/ml)	1.23	1.29
AUC (ng Eq · hr/ml)	1.55	1.37
Total inhibitors		
C_{max} (ng Eq/ml)	1.34	1.54*
AUC (ng Eq · hr/ml)	1.50	1.61*

[a] Geometric mean ratio.
[b] $P < 0.05$.
* Not applicable.

state plasma concentrations of total and active HMG-CoA reductase inhibitors do not appear to be large enough to warrant modifying dosage as a function of either age or gender, because the therapeutic windows for lovastatin and simvastatin are broad (5–8), plasma concentrations of HMG-CoA reductase inhibitors are not necessarily indicative of efficacy, and the overall frequencies of clinical and laboratory adverse events are not higher in the elderly than in younger patients receiving simvastatin (8).

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