Prolonged inhibition of cholesterol synthesis explains the efficacy of atorvastatin

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Abstract HMG-CoA reductase inhibitors or statins are effective in both the primary and secondary prevention of coronary heart disease, the extent of benefit being proportional to the reduction in low density lipoprotein (LDL) cholesterol achieved. Atorvastatin, a newly licensed compound, reportedly lowers LDL with greater efficacy than other statins. The mechanism of this action was, therefore, explored in twenty patients with refractory familial hypercholesterolemia who received in a single-blind sequence simvastatin 40 mg/day, placebo and atorvastatin 10 mg/day each for 4 weeks. At the end of the placebo period the effects of single 40-mg doses of simvastatin and atorvastatin on plasma levels and urinary excretion of mevalonic acid, indices of HMG-CoA reductase activity, were compared. Administration of atorvastatin 10 mg daily for 1 month lowered LDL cholesterol by 32.5%, compared with placebo ($P = 0.0001$), which was 4.5% less than the decrease after simvastatin 40 mg daily ($P = 0.33$). The area under the plasma curve and urinary mevalonic acid/ creatinine ratio were both significantly less during the 24 h after a single dose of atorvastatin 40 mg than after a single dose of simvastatin 40 mg ($P < 0.01$). These findings suggest that the greater efficacy of atorvastatin compared with simvastatin is due to more prolonged inhibition of HMG-CoA reductase, presumably reflecting longer residence of atorvastatin or its active metabolites in the liver.—**Naoumova, R. P., S. Dunn, L. Rallidis, O. Abu-Muhana, C. Neuwirth, N. B. Rendell, G. W. Taylor, and G. R. Thompson.** Prolonged inhibition of cholesterol synthesis explains the efficacy of atorvastatin. *J. Lipid Res.* 1997. **38:** 1496–1500.

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The beneficial effect on coronary heart disease (CHD) of treatment with hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins has become firmly established following the results of three prevention trials, one primary (1) and two secondary (2, 3). Evidence from angiographic studies suggests that the decrease in clinical events seen after 2 years of treatment with simvastatin or pravastatin is preceded by a decreased rate of progression of coronary lesions (4), the extent of benefit depending upon the magnitude of the reduction in low density lipoprotein (LDL) achieved (5). Decreases in LDL cholesterol greater than 40% result in regression of lesions, as shown previously in patients with familial hypercholesterolemia (FH) undergoing treatment with simvastatin combined with either LDL apheresis or anion-exchange resins (6), but this outcome has seldom been observed with statins given alone.

The recent licensing of atorvastatin in Britain, Germany, and the USA means that it is now possible to reduce LDL cholesterol by up to 60% using monotherapy (7). Even patients with homozygous FH, who usually respond poorly to statins, show a 31% decrease in LDL on 80 mg/day of atorvastatin (8) whereas the same dose achieved a 54% decrease in FH heterozygotes (9). The present study compares the efficacy and duration of action of atorvastatin and simvastatin in patients with refractory FH and investigates the mechanism for the reportedly greater efficacy of atorvastatin.

SUBJECTS AND METHODS

Males and females below the age of 65 with heterozygous FH and an LDL cholesterol ≥5 mmol/l despite combination therapy with simvastatin 40 mg daily plus an anion-exchange resin and/or nicotinic acid and/or bezafibrate were eligible for the study. Exclusion criteria were hepatic dysfunction, concurrent therapy with cyclosporin and obesity (BMI > 35). Fifteen male and

Abbreviations: HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; CHD, coronary heart disease; LDL, low density lipoprotein; FH, familial hypercholesterolemia; HDL, high density lipoprotein; MVA, mevalonic acid.

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6 female patients, mean age 51.4 years, 13 with tendon xanthomas and 13 with CHD, were entered into the study. Their mean (SD) LDL cholesterol was 6.85 (1.43) mmol/l and BMI was 27.1 (2.91) kg/m^2. The apoE phenotype was 3/3 in 9, 3/4 in 9, and 2/3 in 3 patients.

After recruitment, patients discontinued all lipid-lowering drugs except simvastatin. One of these patients was excluded owing to difficulties in obtaining blood samples during this phase of the study. In the remaining 20 patients blood samples were taken between 0800 and 0900 hours (after an overnight fast) for measurement of serum total and HDL cholesterol, triglyceride, apolipoprotein (apo) B, lipoprotein[a] (Lp[a]), and plasma mevalonic acid (MVA) before and after 1 month of 40 mg simvastatin each evening, followed by 1 month of placebo, followed by 1 month of 10 mg atorvastatin each evening. LDL cholesterol was calculated according to Friedewald, Levy, and Fredrickson (10). The doses of atorvastatin and simvastatin were designed to achieve similar reductions in LDL cholesterol, based on a previous estimate of their relative efficacy (11). During the final week on placebo, the diurnal rhythm of MVA, an index of cholesterol synthesis (12–14), was determined by assaying plasma levels at intervals during the 24 h after a single dose of placebo (given at 0900 h), and again after single 40-mg doses of simvastatin and atorvastatin, given in random sequence (at 0900 h on the next day and again 3 days later). Urine was collected during each of the three 24-h periods and assayed for MVA and creatinine.

MVA was measured in plasma and urine by gas chromatography–electron capture mass spectrometry, as described previously (9). ApoB and Lp[a] were assayed by immunonephalometry, using a Beckman Array analyzer. ApoE phenotyping was performed by immunoblotting (15).

The study was approved by the Research Ethics Committee of Hammersmith Hospitals NHS Trust and written, informed consent was obtained from all participants.

Statistical analysis

Serum lipid parameters and plasma MVA were compared at the end of each treatment period using analysis of variance. Prior to analysis, triglycerides, Lp[a], and MVA were subjected to a logarithmic transformation.

The effects of a single dose of placebo, simvastatin, and atorvastatin on plasma MVA were assessed by a mixed model analysis of variance. The area under the MVA response by time curve was used as an outcome measure. The Watson test and Bartlett's test were performed to check the equal variance assumption. The order of dosing with simvastatin and atorvastatin had been randomized, which allowed the period effect to be investigated and shown to be nonsignificant. The 24-h urinary excretion of MVA relative to creatinine was assessed by analysis of variance.

TABLE 1. Serum lipids and plasma mevalonic acid (MVA) (mean (SD)) after 1 month each on 40 mg/day simvastatin, placebo, and 10 mg/day atorvastatin

	Simvastatin (40 mg)	Placebo	Atorvastatin (10 mg)
Total cholesterol, mmol/l	8.16 (1.46)	11.84 (1.34)	8.44 (1.42)
Triglyceride, mmol/l	1.64[a]	2.38[a]	1.74[a]
HDL cholesterol, mmol/l	1.18 (0.26)	1.08 (0.25)	1.15 (0.27)
LDL cholesterol, mmol/l	6.17 (1.31)	9.56 (1.16)	6.45 (1.36)
ApoB, mg/dl	179 (41)	264 (34)	197 (40)
Lp[a], mg/dl	29[a]	22[a]	27[a]
MVA, ng/ml	3.25[a]	5.25[a]	3.32[a]

[a]Geometric mean.

RESULTS

Sequential changes in lipid and other variables

Serum levels of lipids and lipoproteins after each 1-month treatment period and the percentage differences between them are shown in **Table 1** and **Table 2.** Serum total and LDL cholesterol, triglyceride, apoB, and MVA levels were lower and HDL cholesterol and Lp[a] levels were higher on both statins as compared with placebo. All the differences between atorvastatin and placebo were highly significant except for HDL cholesterol. Total and LDL cholesterol, triglyceride, apoB, and MVA levels were slightly higher and HDL cholesterol and Lp[a] slightly lower on 10 mg atorvastatin than on 40 mg simvastatin but none of these differences was statistically significant. Decreases in LDL cholesterol on atorvastatin did not differ significantly according to the presence or absence of an ε4 allele (present, −2.71 mmol/l vs. absent, −3.42 mmol/l, $P = 0.098$). No significant differences were observed in the frequency of symptomatic or biochemical side-effects between the three treatment periods.

Acute changes in MVA after single, equal doses of each statin

Figure 1 shows the diurnal rhythm of plasma MVA after a tablet of placebo at 0900 h, which reaches a nadir at 1700 h and peaks at 0200 h. Levels of MVA decreased sharply within 4 h of the administration of 40 mg of either simvastatin or atorvastatin and remained suppressed for a further 4 h. However, thereafter MVA levels increased to a greater extent after simvastatin than after atorvastatin, the area under the curve after the latter being significantly less than after the former.

The more prolonged action of atorvastatin in suppressing cholesterol synthesis was confirmed by the sig-

TABLE 2. Mean percentage changes with 95% confidence intervals (CI) after 1 month of 10 mg/day atorvastatin compared with placebo and 40 mg/day simvastatin

	Versus Placebo	95% CI	P	Versus Simvastatin, 40 mg	95% CI	P
	%	%		%	%	
Total cholesterol	−28.7	−33.5 to −24.0	0.0001	3.5	−3.4 to 10.4	0.32
Triglyceride[a]	−27.2	−37.5 to −15.3	0.0001	5.7	−9.2 to 23.0	0.47
HDL cholesterol	5.7	−1.0 to 12.4	0.10	−3.0	−9.1 to 3.1	0.35
LDL cholesterol	−32.5	−38.4 to −26.6	0.0001	4.5	−4.6 to 13.7	0.33
ApoB	−26.5	−33.3 to −19.7	0.0001	6.7	−3.4 to 17.3	0.19
Lp[a][a]	20.0	5.4 to 36.6	0.007	−7.8	−18.9 to 5.0	0.22
MVA[a]	−36.8	−47.3 to −24.2	0.0001	2.1	−14.9 to 20.2	0.82

[a]Percent change in geometric mean.

nificantly lower ratio of urinary MVA to creatinine, reflecting decreased excretion of MVA, after atorvastatin 40 mg (0.106 ± 0.007) as compared with both placebo (0.180 ± 0.012, $P = 0.0001$) and simvastatin 40 mg (0.127 ± 0.008, $P = 0.01$) (**Fig. 2**).

DISCUSSION

This short-term study was aimed at assessing the effectiveness and mechanism of action of atorvastatin in subjects who were deliberately chosen because of their refractory hypercholesterolemia. Despite this circumstance, single-blind administration of 10 mg daily atorvastatin for 1 month decreased LDL cholesterol by 33% more than placebo. This was approximately 5% less than the corresponding decrease achieved by 40 mg simvastatin daily. Although the difference between the two drugs in LDL-lowering was not statistically significant, our findings suggest that 10 mg atorvastatin is equivalent to a dose of simvastatin between 20 and 40 mg daily.

One of the chief objectives of the study was to explain the greater efficacy of atorvastatin compared with other compounds of this class, as previously reported (11). This was investigated by measuring plasma levels and urinary excretion of MVA during the 24 h after single, equal doses of atorvastatin and simvastatin, with a gap of 3 days between each statin. The validity and usefulness of plasma and urinary MVA as semi-quantitative markers of changes in cholesterol synthesis have been reviewed recently (16, 17). Our results show that both statins suppress cholesterol synthesis to a similar extent over the first 8 h after administration but demonstrate that this effect lasts significantly longer after atorvastatin. This may explain why 40 mg/day atorvastatin decreases LDL cholesterol by 50%, as compared with the 40% decrease seen with the same dose of simvastatin, and why atorvastatin can be given at any time of the day (11) whereas simvastatin is more effective when given in the evening (18), HMG-CoA reductase activity being maximal during the night (12).

The more marked the decrease in cholesterol synthesis the greater would be the expected increase in receptor-mediated LDL catabolism and the decrease in LDL production; both mechanisms appear to contribute to the LDL-lowering property of statins (19). The superior ability of atorvastatin to lower LDL is not attributable to its properties as a competitive inhibitor of HMG-CoA

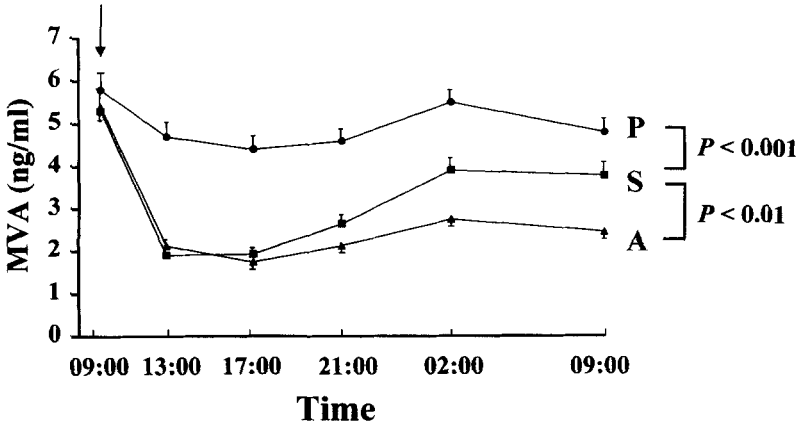

Fig. 1. Comparison of effect of single dose of placebo, 40 mg simvastatin, and 40 mg atorvastatin on plasma mevalonate (mean and SE) in FH heterozygotes ($n = 20$). Arrow shows time of administration of placebo (P), simvastatin (S), and atorvastatin (A).

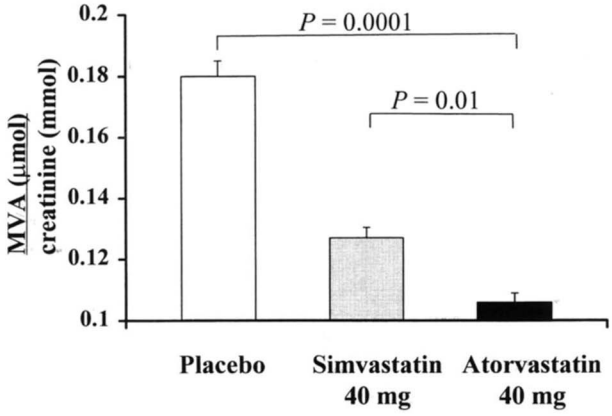

Fig. 2. 24-H urinary MVA:creatinine ratio (mean and SE) after a single dose of placebo, 40 mg simvastatin, and 40 mg atorvastatin in FH heterozygotes (n = 20).

reductase, which are similar to other statins (20), but probably reflects its greater uptake and longer duration of action in the liver (21). These properties could explain the prolonged decrease in MVA that we observed during the 24 h after a single dose of atorvastatin. In addition to its cholesterol-lowering properties, atorvastatin has also been shown to reduce serum triglycerides by over 40% (22) which is more than has been documented with recommended maximal doses of other statins. The decrease in triglycerides probably reflects either reduced secretion of very low density lipoprotein (VLDL), consequent upon the decreased availability of cholesterol ester for VLDL assembly in the liver (16), or increased hepatic removal of triglyceride rich-VLDL (23).

There is now ample evidence that lovastatin, simvastatin, and pravastatin all beneficially influence the pathology and clinical consequences of coronary atherosclerosis by lowering LDL. Preliminary data suggest that fluvastatin, the least potent of the four in that respect, exerts a similar impact (24), which is suggestive of a class effect. If so, given its greater potential for both LDL and triglyceride lowering, atorvastatin should prove to be as, or even more, effective than other statins in preventing CHD.

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